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Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Sixth Special Issue

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The American Society for Apheresis (ASFA) JCA Special Issue Writing Committee is charged with reviewing, updating and categorizating indications for therapeutic apheresis. Beginning with the 2007 ASFA Special Issue (Fourth Edition), the committee has incorporated systematic review and evidence-based approach in the grading and categorization of indications. This Sixth Edition of the ASFA Special Issue has further improved the process of using evidence-based medicine in the recommendations by consistently applying the category and GRADE system definitions, but eliminating the "level of evidence" criteria (from the University HealthCare Consortium) utilized in prior editions given redundancy between GRADE and University HealthCare Consortium systems. The general layout and concept of a fact sheet that was utilized in the Fourth and Fifth Editions, has been largely maintained in this edition. Each fact sheet succinctly summarizes the evidence for the use of therapeutic apheresis in a specific disease entity. This article consists of 78 fact sheets (increased from 2010) for therapeutic indications in ASFA categories I through IV, with many diseases categorized having multiple clinical presentations/situations which are individually graded and categorized. J. Clin. Apheresis 28:145–284, 2013. © 2013 Wiley Periodicals, Inc.

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INTRODUCTION

With great pleasure, we present to you the American Society for Apheresis (ASFA) Special Issue 2013 (also known as the Sixth Edition of the ASFA Special Issue). After more than 1.5 years of engaging work and rigorous critical review of fact sheets, we believe that this document will appeal to both practitioners of apheresis medicine and other physicians who may need to utilize therapeutic apheresis for the care of their patients. This third iteration of evidence-based ASFA categories are based upon stringent review of up-to-date literature, analysis of the quality of evidence, and strength of recommendation derived from this evidence.

This evidence-based approach is designed to achieve several objectives. First, it provides uniformity to ASFA category assignment and disease discussion while minimizing personal bias; second, it provides the strength of recommendation; 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 IV. This is a notable change from prior editions where category IV indication fact sheets were compiled in a separate document or not published. With the newer approach, the Sixth Edition is able to present in full detail the evidence that supports the ASFA category IV designation of specific disease processes in a single document for greater ease of use. Given the utility of the table format used in prior editions to summarize disease name, special condition(s), apheresis modality(ies), ASFA category, and GRADE of recommendation, we have continued to use it in this edition. Therapeutic apheresis procedures considered in this publication and included in the fact sheets are therapeutic plasma exchange (TPE), erythrocytapheresis, red blood cell (RBC) exchange, thrombocytapheresis, leukocytapheresis, extracorporeal photopheresis (ECP), immunadsorption (IA), LDL apheresis, adsorptive cytapheresis, and rheopheresis.

The 2013 JCA Special Issue Writing Committee consisted of 10 members from diverse fields including Transfusion Medicine/Apheresis, Hematology/Oncology and Nephrology, and from diverse geographies throughout the continental United States (US). Diseases for which publications in the literature describe the use of apheresis as treatment were reviewed by a primary author who enumerated and distilled the literature and created a fact sheet summarizing the disease incidence, description, management, rationale, technical notes, volumes treated, replacement fluids used, treatment frequency, optimal duration of therapeutic apheresis, and references. This first draft was reviewed by two other committee members, followed by outside specialist review for select fact sheets. These finalized fact sheets were then categorized and graded. Categorization and grading definitions were assigned in the same manner as in the Fifth Edition, but the application to each disease was applied more specifically and consistently. "Level of evidence" recommendations (criteria utilized by the University HealthCare Consortium) were not included in the fact sheet given redundancy with GRADE recommendations used to evaluate the quality of studies [1]. The number of diseases/medical conditions categorized increased from 68 to 78 from the JCA 2010 special edition to the current edition. New fact sheets include Henoch-Schönlein purpura (TPE: crescentric category III/grade 2C, severe extrarenal disease III/2C), heparin induced thrombocytopenia (TPE: precardiopulmonary bypass III/2C, thrombosis III/2C), IgA nephropathy (TPE: crescentic III/2B, chronic progressive III/2C), lipoprotein(a) hyperlipoproteinemia (LDL apheresis: II/1B), peripheral vascular disease (LDL apheresis: III/2C), sudden sensorineural hearing loss (LDL apheresis: III/2A, rheopheresis: III/2A, TPE: III/2C), toxic epidermal necrolysis (TPE: III/2B) and voltage gated potassium channel antibodies (TPE: II/1C). Factsheets on ABO-incompatible (ABOi) solid organ transplantation and hemolytic uremic syndrome (HUS) were separated into ABOi renal and liver transplantation, and atypical and infection-associated HUS, respectively. This was done to allow for a more complete presentation of published studies and discussion of treatment recommendations in these areas. Several fact sheets have been significantly updated to reflect the use of apheresis in varied settings in the same disease/medical condition. Examples include the fact sheet on ABO-compatible cardiac transplantation which now includes information on the use of TPE in the setting of desensitization in patients with high levels of HLA alloantibodies, and in the lung allograft rejection fact sheet which now includes information on the use of TPE in the setting of humoral rejection. Twenty three new disease state/condition categories are included in the 2013 compared to the 2010 Special Issue. Ten new disease state/condition are included based upon new treatments of previously categorized diseases, in addition to numerous changes to categorization and recommendation GRADE.

METHODOLOGY

Evidence-Based Approach

The ASFA Special Issue 2007 incorporated evidence-based medicine into well-defined and widely accepted ASFA Categories and quality of evidence [2]. In the ASFA Special Issue 2010, this system was modified to revise category definitions, maintain quality of the evidence, and add strength of the recommendation [1]. In the ASFA Special Issue 2013, this has been further refined to provide information on

TABLE I. Indications for Therapeutic Apheresis–ASFA 2013 Categories [1]

Category	Description
I	**Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.** *Example: plasma exchange in Guillain-Barre syndrome as 1st-line standalone therapy; plasma exchange in myasthenia gravis as 1st-line in conjunction with immunosuppression and cholinesterase inhibition*
II	**Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.** *Example: plasma exchange as standalone secondary treatment for acute disseminated encephalomyelitis after high-dose IV corticosteroid failure; extracorporeal photopheresis added to corticosteroids for unresponsive chronic graft-versus-host disease*
III	**Optimum role of apheresis therapy is not established. Decision making should be individualized**. *Example:extracorporeal photopheresis for nephrogenic systemic fibrosis; plasma exchange in patients with sepsis and multi-organ failure*
IV	**Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.** *Example: plasma exchange for active rheumatoid arthritis*

categorization (Table I), and strength of recommendation based on the GRADE system, which takes methodological quality of supporting evidence into account (Table II), while eliminating the need for "Level of Evidence" information used in previous fact sheets.

ASFA Categories

The definitions of the four ASFA categories in the Sixth Edition remain unchanged from the definitions used in the Fifth Edition (Table I). This allowed us to continue to categorize disease states in alignment with grading recommendation, which in turn takes into account the quality of published evidence in the literature.

Grade of Recommendation

The committee recognizes that despite these enhancements in ASFA fact sheets based upon grading recommendations and systematic review of the literature, the grading evidence may still be difficult to translate into clinical practice. This challenge has been an issue for many groups working on clinical recommendations and guidelines. Several organizations implemented the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence. The system is generally user friendly as shown in multiple publications [3–7]. In the Fifth Edition, the GRADE system was used to assign recommendation grades for therapeutic apheresis to enhance the clinical value of ASFA categories, and we have continued this in the Sixth Edition. Table II contains abbreviated principles of grading

TABLE II. Grading Recommendations adopted from Guyatt and coworkers [8].

Recommendation	Description	Methodological quality of supporting evidence	Implications
Grade 1A	Strong recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1B	Strong recommendation, moderate quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1C	Strong recommendation, low-quality or very low- quality evidence	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
Grade 2A	Weak recommendation, high quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients'or societal values
Grade 2B	Weak recommendation, moderate-quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2C	Weak recommendation, low-quality or very low-quality evidence	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

TABLE III. Modified McLeod's Criteria for Evaluation of Therapeutic Apheresis Efficacy [9]

Evidence	McLeod's criteria	Explanation
Mechanism	"Plausible Pathogenesis"	The current understanding of the disease process supports a clear rationale for the use of therapeutic apheresis modality.
Correction	"Better Blood"	The abnormality, which makes therapeutic apheresis plausible, can be meaningfully corrected by its use.
Clinical Effect	"Perkier Patients"	There is a strong evidence that therapeutic apheresis confers benefit that is clinically worthwhile, and not just statistically significant.

recommendations derived from Guyatt and coworkers [8]. It is important to note that the grade can be used in support or against the use of any particular therapeutic modality. Hence, weak recommendations, such as Grade 2C, are more likely to be affected by additional evidence of higher quality than strong recommendations based on high quality of evidence (e.g., Grade 1A). The quality of published evidence can be affected by a number of factors [8]. For example, the quality of evidence based on a randomized controlled trial (RCT) can be significantly diminished by poor quality of planning and implementation of the RCTs suggesting a high likelihood of bias; inconsistency of results; indirectness of evidence; and/or sparse outcome data. Similarly, the quality of evidence based on observational studies can be increased by an effect of large magnitude induced by apheresis. The members of the Committee took these variables into consideration while grading and categorizing disease indications.

Design of the Fact Sheet

The 2013 JCA Special Issue Writing Committee made minimal changes in the design of the fact sheet from the Fifth Special Issue [1]. The most important modification was removal of level of evidence as described above. 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 as substantial condensing of available information was required to achieve this user friendly format. The updated references provided are not meant to be exhaustive but rather to serve as a starting point in a search for more information. New to this edition, the authors of the fact sheets could provide as many references as they desired and the references are organized by fact sheet (and some subheaders) for easier access.

ASFA Category Assignments for 2013

The process for ASFA category assignment developed for previous editions has largely been maintained, and enhanced by stringent application of evidence based criteria to ensure consistency within and across fact sheets. The committee-based approach is comprehensive and systematic in assembling objective evidence for disease indications, with strength of recommendation based upon the quality of the evidence [1]. The JCA Special Issue Writing Committee consisting of 10 ASFA members was established in 2011. The group was asked to review, revise, and amend indications for therapeutic apheresis. The membership of ASFA was also polled for new disease indications reportably treated by apheresis that had previously not been categorized.

The process of developing new and amending old indications consisted of four steps (Fig. 2). Step I created a list of diseases to be included. Step II assigned each of the working group members 7–10 indications to review. At a minimum, the review consisted of identifying all articles published in the English language, which described the use of therapeutic apheresis. Step III consisted of circulating the first draft (Draft I) of the fact sheet to two other members of the Committee for editorial comments. On the basis of these comments the author created Draft II. In step IV, all fact sheets were finalized and each disease/condition was assigned an ASFA category and grade of recommendation at a face-to-face meeting and conference calls of the Committee in 2012. The category assignment and recommendation grade were based upon the literature review and determined by consensus of all committee members. There was a thorough discussion with a final consensus or anonymous voting on the diseases/conditions without agreement on category assignment. Additionally, the members of the Committee were encouraged to use ''McLeod's Criteria'' to assess indication, which are summarized in a modified form in Table III [9]. We encourage practitioners of apheresis medicine to use these criteria when considering the use of therapeutic apheresis in a medical condition which may yet to be categorized by ASFA. However, the recommendation grade added additional and likely critical dimension to evaluation of clinical benefit of therapeutic apheresis in reviewed diseases. ASFA category and grade of recommendation are summarized in Table IV. In the Sixth Edition, within each disease fact sheet, if more than one type of apheresis modality was used, or if

TABLE IV. ASFA 2013 Indication Categories for Therapeutic Apheresis

Disease name	TA Modality	Disease condition	Category	Grade
Acute disseminated encephalomyelitis	TPE		II	2C
Acute inflammatory demyelinating polyneuropathy (Guillain-Barre Syndrome)	TPE		I	1A
	TPE	Post IVIG	III	2C
Acute liver failure	TPE		III	2B
Age related macular degeneration, dry	Rheopheresis		I	1B
Amyloidosis, systemic	TPE		IV	2C
Amyotrophic lateral sclerosis	TPE		IV	1C
ANCA- associated rapidly progressive glomerulonephritis (Granulomatosis with polyangiitis; Wegener's Granulomatosis)	TPE	Dialysis dependence	I	1A
	TPE	DAH	I	1C
	TPE	Dialysis independence	III	2C
Anti-glomerular basement membrane disease (Goodpasture's syndrome)	TPE	Dialysis dependent and no DAH	III	2B
	TPE	DAH	I	1C
	TPE	Dialysis independence	I	1B
Aplastic anemia; pure red cell aplasia	TPE	Aplastic anemia	III	2C
	TPE	Pure red cell aplasia	III	2C
Autoimmunic hemolytic anemia: WAHA; cold agglutinin disease	TPE	Severe WAHA	III	2C
	TPE	Severe cold agglutinin disease	II	2C
Babesiosis	RBC exchange	Severe	I	1C
	RBC exchange	High-risk population	II	2C
Burn shock resuscitation	TPE		III	2B
Cardiac transplantation	ECP	Rejection prophylaxis	II	2A
	ECP	Cellular or recurrent rejection	II	1B
	TPE	Desensitization, positive cross-match due to donor specific HLA antibody	III	2C
	TPE	Antibody mediated rejection	III	2C
Catastrophic antiphospholipid syndrome	TPE		II	2C
Chronic focal encephalitis (Rasmussen Encephalitis)	TPE		III	2C
	IA		III	2C
Chronic inflammatory demyelinating polyradiculoneuropathy	TPE		I	1B
Coagulation factor inhibitors	TPE	Alloantibody	IV	2C
	IA	Alloantibody	III	2B
	TPE	Autoantibody	III	2C
	IA	Autoantibody	III	1C
Cryoglobulinemia	TPE	Symptomatic/severe	I	2A
	IA	Symptomatic/severe	II	2B
Cutaneous T-cell lymphoma; mycosis fungoides; Sezary syndrome	ECP	Erythrodermic	I	1B
	ECP	Non-erythrodermic	III	2C
Dermatomyositis or polymyositis	TPE		IV	2A
	Leukocytapheresis		IV	2A
Dilated cardiomyopathy, idiopathic	TPE	NYHA II-IV	III	2C
	IA	NYHA II-IV	II	1B
Famalial hypercholesterolemia	LDL apheresis	Homozygotes	I	1A
	LDL apheresis	Heterozygotes	II	1A
	TPE	Homozygotes with small bood volume	II	1C
Focal segmental glomerulosclerosis	TPE	Recurrent in transplanted kidney	I	1B
Graft-versus-host disease	ECP	Skin (chronic)	II	1B
	ECP	Skin (acute)	II	1C

TABLE IV. *Continued*

Disease name	TA Modality	Disease condition	Category	Grade
	ECP	Non-skin (acute/chronic)	III	2B
HSCT, ABO incompatible	TPE	Major HPC, Marrow	II	1B
	TPE	Major HPC, Apheresis	II	2B
	RBC exchange	Minor HPC, Apheresis	III	2C
Hemolytic uremic syndrome, atypical	TPE	Complement gene mutations	II	2C
	TPE	Factor H antibodies	I	2C
	TPE	MCP mutations	IV	1C
Hemolytic uremic syndrome,infection-associated	TPE	Shiga toxin associated	IV	1C
	TPE	S. pneumonae associated	III	2C
Henoch-Schonlein purpura	TPE	Crescentric	III	2C
	TPE	Severe extrarenal disease	III	2C
Heparin induced thrombocytponia	TPE	Pre-cardiopulmonary bypass	III	2C
	TPE	Thrombosis	III	2C
Heritary hemachromatosis	Erythrocytapheresis		I	1B
Hyperleukocytosis	Leukocytapheresis	Leukostasis	I	1B
	Leukocytapheresis	Prophylaxis	III	2C
Hypertriglyceridemic pancreatitis	TPE		III	2C
Hyperviscosity in monoclonal gammopathies	TPE	Symptomatic	I	1B
	TPE	Prophylaxis for rituximab	I	1C
Immune complex rapidly progressive glomerulonephritis	TPE		III	2B
Immune thrombocytopenia	TPE	Refractory	IV	2C
	IA	Refractory	III	2C
Immunoglobin A nephropathy	TPE	Crescentic	III	2B
	TPE	Chronic progressive	III	2C
Inclusion body myositis	TPE		IV	2C
	Leukocytapheresis		IV	2C
Inflammatory bowel disease	Adsorptive cytapheresis	Ulcerative colitis	III/II	1B/2B
	Adsorptive cytapheresis	Crohn's disease	III	1B
	ECP	Crohn's disease	III	2C
Lambert-Eaton myasthenic syndrome	TPE		II	2C
Liprotein (a) hyperlipoproteinemia	LDL apheresis		II	1B
Liver transplantation, ABO incompatible	TPE	Desensitization, live donor	I	1C
	TPE	Desensitization, deceased donor	III	2C
	TPE	Humoral Rejection	III	2C
Lung allograft rejection	ECP	Bronchiolitis obliterans syndrome	II	1C
	TPE	Antibody mediated rejection	III	2C
Malaria	RBC exchange	Severe	II	2B
Multiple Sclerosis	TPE	Acute CNS inflammatory demyelinating disease	II	1B
	IA	Acute CNS inflammatory demyelinating disease	III	2C
	TPE	Chronic progressive	III	2B
Myasthenia gravis	TPE	Moderate-severe	I	1B
	TPE	Pre-thymectomy	I	1C
Myeloma cast nephropathy	TPE		II	2B
Nephrogenic sytemic fibrosis	ECP		III	2C
	TPE		III	2C
Neuromyelitis optica (Devic's syndrome)	TPE	Acute	II	1B
	TPE	Maintenance	III	2C
Overdose, envenomation and poisoning	TPE	Mushroom poisoning	II	2C
	TPE	Envenomation	III	2C

TABLE IV. *Continued*

Disease name	TA Modality	Disease condition	Category	Grade
	TPE	Natalizumab & PML	III	2C
	RBC exchange	Tacrolimus	III	2C
Paraneoplastic neurological syndromes	TPE		III	2C
	IA		III	2C
Paraproteinemic demyelinating polyneuropahties	TPE	IgG/IgA	I	1B
	TPE	IgM	I	1C
	TPE	Multiple myeloma	III	2C
	IA	IgG/IgA/IgM	III	2C
PANDAS; sydenham's chorea	TPE	PANDAS exacerbation	I	1B
	TPE	Sydenham's chorea	I	1B
Pemphigus vulgaris	TPE	Severe	III	2C
	ECP	Severe	III	2C
	IA	Severe	III	2C
Peripheral vascular diseases	LDL apheresis		III	2C
Phytanic acid storage disease (Refsum's disease)	TPE		II	2C
	LDL apheresis		II	2C
Polycythemia vera and erythrocytosis	Erythrocytapheresis	Polycythemia vera	I	1B
	Erythrocytapheresis	Secondary erythrocytosis	III	1C
POEMS syndrome	TPE		IV	1C
Post transfusion purpura	TPE		III	2C
Psoriasis	TPE		IV	2C
	Adsorptive cytapheresis	Disseminated pustular	III	2C
	Lymphocytapheresis		III	2C
	ECP		III	2B
Red cell alloimmunization in pregnancy	TPE	Prior to IUT availability	III	2C
Renal transplantation, ABO compatible	TPE	Antibody mediated rejection	I	1B
	TPE	Desensitization, living donor, positive crossmatch due to donor specific HLA antibody	I	1B
	TPE	Desensitization, high PRA deceased donor	III	2C
Renal transplantation, ABO incompatible	TPE	Desensitization, live donor	I	1B
	TPE	Humoral rejection	II	1B
	TPE	Group A2/A2B into B, deceased donor	IV	1B
Schizophrenia	TPE		IV	1A
Scleroderma (Progressive systemic sclerosis)	TPE		III	2C
	ECP		III	2B
Sepsis with multiorgan failure	TPE		III	2B
Sickle cell disease, acute	RBC exchange	Acute stroke	I	1C
	RBC exchange	Acute chest syndrome, severe	II	1C
	RBC exchange	Priapism	III	2C
	RBC exchange	Multi-organ failure	III	2C
	RBC exchange	Splenic sequestration; hepatic sequestration; intrahepatic cholestasis	III	2C
Sickle cell disease, non-acute	RBC exchange	Stroke prophylaxis/ iron overload prevention	II	1C
	RBC exchange	Vaso-occlusive pain crisis	III	2C
	RBC exchange	Pre-Op management	III	2A
Stiff-person syndrome	TPE		III	2C

TABLE IV. *Continued*

Disease name	TA Modality	Disease condition	Category	Grade
Sudden sensorineural hearing loss	LDL apheresis		III	2A
	Rheopheresis		III	2A
	TPE		III	2C
Systemic lupus erythematosus	TPE	Severe	II	2C
	TPE	Nephritis	IV	1B
Thrombocytosis	Thrombocytapheresis	Symptomatic	II	2C
	Thrombocytapheresis	Prophylactic or secondary	III	2C
Thrombotic microangiopathy, drug associated	TPE	Ticlopidine	I	1B
	TPE	Clopidogrel	III	2B
	TPE	Cyclosporine/ Tacrolimus	III	2C
	TPE	Gemcitabine	IV	2C
	TPE	Quinine	IV	2C
Thrombotic microangiopathy, HSCT associated	TPE	Refractory	III	2C
Thrombotic thrombocytopenic purpura	TPE		I	1A
Thyroid storm	TPE		III	2C
Toxic epidermal necrolysis	TPE	Refractory	III	2B
Voltaged gated potassium channel antibodies	TPE		II	1C
Wilson disease	TPE	Fulminant	I	1C

DAH = diffuse alveolar hemorrhage; HSCT = hematopoietic stem cell transplant; PANDAS = pediatric autoimmune neuropsychiatric disorders associated with streptoccal infections; POEMS = polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes; PML = progressive multifocal leukoencephalopahty; WAHA = warm autoimmune hemolytic anemia.

apheresis was used in more than one clinical setting in the same disease, each was treated as a separate indication and was assigned a recommendation grade and category. As an example, the ABO incompatible renal transplantation fact sheet TPE application was categorized/graded as I/1C for desensitization—live donor, II/1B for humoral rejection and IV/1B for ABO subtype A2/A2B donors into group B recipients—deceased donor. Providing this level of detail to apheresis practitioners is expected to provide in-depth clinical practice information tools to practitioners which will enable them to utilize apheresis in the various complex settings encountered within a specific disease state. The relationship between the ASFA categories and recommendation grades is illustrated in Figure 3. All categorized indications (i.e., ASFA category I through IV) were analyzed after the Committee completed its work. The assigned categories and their respective recommendation grades were plotted. There is a significant expansion in the number of indications (relative to the number of diseases categorized) and is caused by some diseases having several categories and recommendation grades due to multiple disease state/ condition indications within the same disease. The majority of category I indications have recommendation grades of 1A–C. Category II indications are spread through the entire spectrum of recommendation grades, while category III has no indications with highest grade (1A). It can be easily appreciated that ASFA category III indications have the highest number of Grade 2B and Grade 2C recommendations (i.e., the weakest recommendations). This figure illustrates ASFA categorization being firmly grounded in evidence-based medicine.

General Considerations

There are textbooks in the field of apheresis medicine which users of the Special Issue may find useful, including Apheresis: Principles and Practice, Third Edition [10]. The format of the Special Issue restricts the amount of information which can be provided in each fact sheet. In Table V, we propose information that may be included in a consultation note before performing an apheresis procedure. This standard approach to consultation may be helpful to readers who have less experience in the field of apheresis medicine. An area of potential concern for the apheresis practitioner is type of replacement fluid to be used during therapeutic apheresis, particularly TPE. If stated in the fact sheet that TPE is performed daily, after a few days of TPE replaced with albumin, replacement of plasma may be indicated as part of replacement fluid to prevent or treat severe coagulopathy from repetitive removal of coagulation factors through serial TPE in patients whose clinical situation indicate that this is necessary. Plasma supplementation should be performed as the final portion of

TABLE V. General Issues to be Considered When Evaluating a New Patient for Therapeutic Apheresis Initiation

General	Description
Rationale[a]	Based on the established/presumptive diagnosis and history of present illness the discussion could include the rationale for the procedure, brief account of the results of published studies, and patient-specific risks from the procedure.
Impact	The effect of therapeutic apheresis on comorbidities and medications (and vice-versa) should be considered.
Technical issues[a]	The technical aspects of therapeutic apheresis such as type of anticoagulant, replacement solution, vascular access, and volume of whole blood processed (e.g., number of plasma volumes exchanged) should be addressed.
Therapeutic plan[a]	Total number and/or frequency of therapeutic apheresis procedures should be addressed.
Clinical and/or laboratory end-points[a]	The clinical and/or laboratory parameters should be established to monitor effectiveness of the treatment. The criteria for discontinuation of therapeutic apheresis should be discussed whenever appropriate.
Timing and Location	The acceptable timing of initiation of therapeutic apheresis should be considered based on clinical considerations (e.g., medical emergency, urgent, routine etc). The location where the therapeutic apheresis will take place should be also addressed (e.g., intensive care unit, medical ward, operating room, outpatient setting). If the timing appropriate to the clinical condition and urgency level cannot be met, a transfer to a different facility should be considered based on the clinical status of the patient.

NOTE: The above issues should be considered in addition to a routine note addressing patient's history, review of systems and physical examination.
[a]ASFA Fact Sheet for each disease could be helpful in addressing these issues.

the replacement fluid if this is done (e.g., the last 500–1000 mL). Lastly, issues related to the timing of procedures, such as emergency (within hours), urgent (within a day), and routine, are not addressed directly in the fact sheets given the heterogeneity of patient disease presentation. The patient's clinical condition and diagnosis should be carefully evaluated when determining the optimal timing of apheresis therapy. This determination should be made through consultation between the requesting physician and the physician administering apheresis using appropriate medical judgment. The authors hope that the expanded and refined JCA Special Edition provides useful information to inform practitioners about the evidence available, and the recommendations for the use of therapeutic apheresis in a wide range of conditions and disease states.

Glossary

Therapeutic apheresis procedures considered in this publication and included in the fact sheets are TPE, RBC exchange, erythrocytapheresis, thrombocytapheresis, leukocytapheresis, extracorporeal photopheresis (ECP), IA, LDL apheresis, adsorptive cytapheresis, filtration selective removal and rheopheresis. We attempted to summarize definitions of most commonly performed procedures in Table VI.

TABLE VI. Apheresis Procedure Definitions

Procedure/term	Definition
Adsorptive cytapheresis	A therapeutic procedure in which blood of the patient is passed through medical device, which contains a column or filter that selectively adsorbs activated monocytes and granulocytes, allowing the remaining leukocytes and other blood components to be returned to the patient.
Apheresis	A procedure in which blood of the patient or donor is passed through a medical device which separates out one or more components of blood and returns remainder with or without extracorporeal treatment or replacement of the separated component.
Extracorporeal photopheresis (ECP)	A therapeutic procedure in which buffy coat, separated from patient's blood, is treated extracorporeally with a photoactive compound (e.g., psoralens) and exposed to ultraviolet A light and subsequently reinfused to the patient during the same procedure.
Erythrocytapheresis	A procedure in which blood of the patient or donor is passed through a medical device which separates RBCs from other components of blood, the RBCs are removed and replaced with crystalloid or colloid solution, when necessary.
Filtration selective removal	A procedure which uses a filter to remove components from the blood based upon size. Depending upon the pore size of the filters used, different components can be removed. Filtration based instruments can be used to perform plasma exchange or LDL apheresis. They can also be used to perform donor plasmapheresis where plasma is collected for transfusion or further manufacture.
Immunoadsorption (IA)	A therapeutic procedure in which plasma of the patient, after separation from the blood, is passed through a medical device which has a capacity to remove immunoglobulins by specifically binding them to the active component (e.g., Staphylococcal protein A) of the device.
LDL Apheresis	The selective removal of low density lipoproteins from the blood with the return of the remaining components. A variety of instruments are available which remove LDL cholesterol based upon charge (dextran sulfate and polyacrylate), size (double-membrane filtration), precipitation at low pH (HELP), or immunoadsorption with anti-Apo B-100 antibodies.
Leukocytapheresis (LCP)	A procedure in which blood of the patient or the donor is passed through a medical device which separates out white blood cells (e.g., leukemic blasts or granulocytes), collects the selected cells and returns remainder of the patient's or the donor's blood with or without addition of replacement fluid such as colloid and/or crystalloid solution. This procedure can be used therapeutically or in preparation of blood components.
Therapeutic Plasma exchange (TPE)	A therapeutic procedure in which blood of the patient is passed through a medical device which separates out plasma from other components of blood, the plasma is removed and replaced with a replacement solution such as colloid solution (e.g., albumin and/or plasma) or combination of crystalloid/colloid solution.
Plasmapheresis	A procedure in which blood of the patient or the donor is passed through a medical device which separates out plasma from other components of blood and the plasma is removed (i.e., less than 15% of total plasma volume) without the use of replacement solution.
Plateletapheresis	A procedure in which blood of the donor is passed through a medical device which separates out platelets, collects the platelets and returns remainder of the donor's blood. This procedure is used in preparation of blood components (e.g., apheresis platelets).
RBC exchange	A therapeutic procedure in which blood of the patient is passed through a medical device which separates RBCs from other components of blood, the RBCs are removed and replaced with donor RBCs alone and colloid solution.
Rheopheresis	A therapeutic procedure in which blood of the patient is passed through a medical device which separates out high-molecular weight plasma components such as fibrinogen, α2-macroglobulin, low-density lipoprotein cholesterol, and IgM in order to reduce plasma viscosity and red cell aggregation. This is done to improve blood flow and tissue oxygenation. LDL apheresis devices and selective filtration devices utilizing two filters, one to separate plasma from cells and a second to separate the high-molecular weight components, are used for these procedures.
Therapeutic apheresis (TA)	A therapeutic procedure in which a blood of the patient is passed through an extracorporeal medical device which separates components of blood to treat a disease. This is a general term which includes all apheresis based procedures used therapeutically.
Thrombocytapheresis	A therapeutic procedure in which blood of the patient is passed through a medical device which separates out platelets, removes the platelets and returns remainder of the patient's blood with or without addition of replacement fluid such as colloid and/or crystalloid solution.

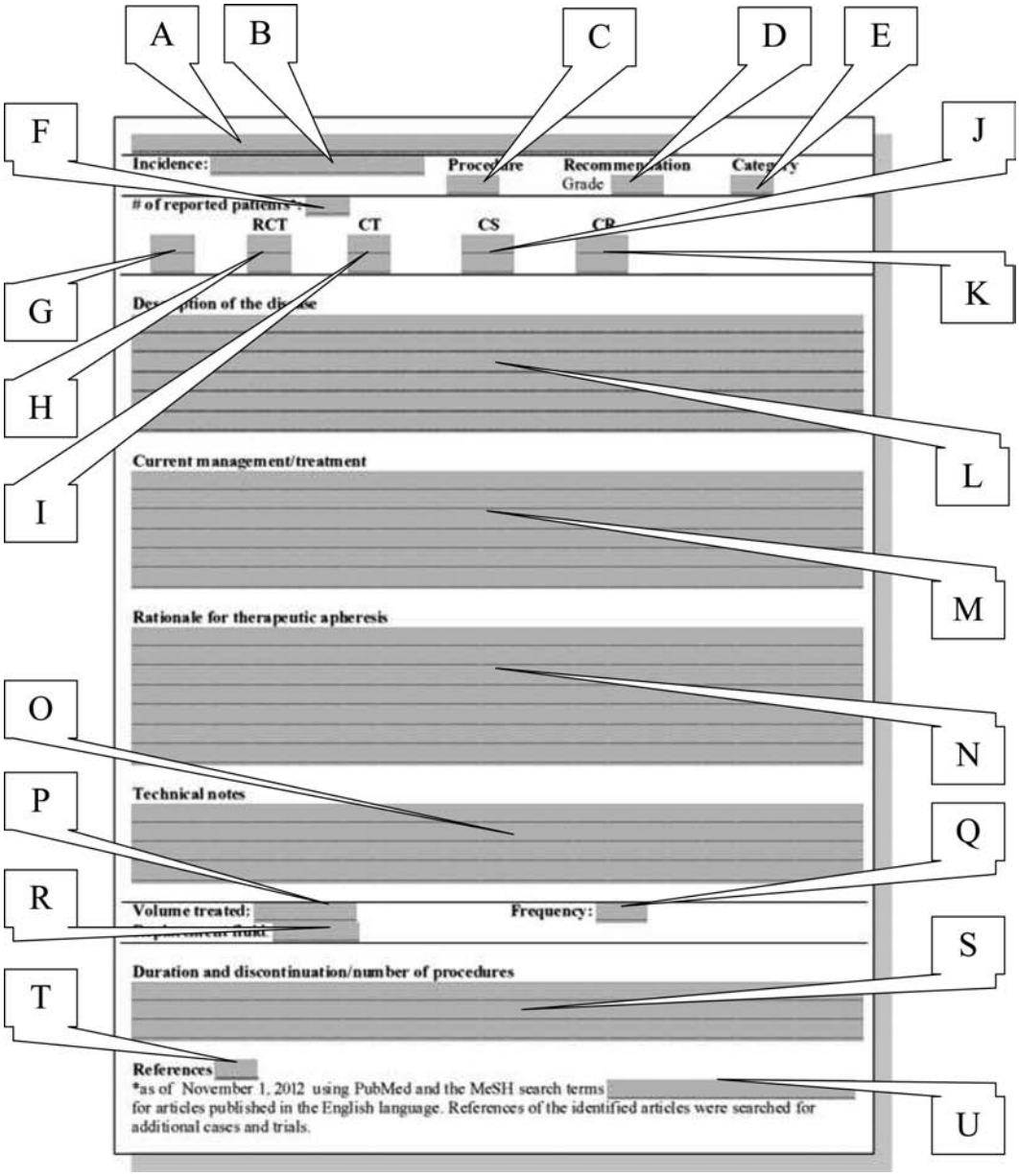

Fig. 1. Explanation of the fact sheet used in the ASFA Special Issue, Sixth Edition (2013).

A The name of the disease as well as its eponym when appropriate.

B This section lists the incidence and/or prevalence of the disease in the US and other selected geographic regions, 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 incidence or prevalence, other terms, such as rare, infrequent or unknown are used. The reader is cautioned to use this information only as a general indicator of disease prevalence. For some diseases, prevalence may vary by geographical area.

C The type of therapeutic apheresis procedure is listed here. For certain diseases there are several apheresis based modalities available. In such instances (e.g., lung allograft rejection) more than one type of therapeutic apheresis modality is listed.

D Recommendation grade is assigned to each categorized entity. As noted in the text the authors used the Grading of Recommendations Assessment Development and Evaluation (GRADE) system for grading clinical recommendations level. For example, Grade 1B implies strong recommendation based on moderate quality evidence, whereas 2C refers to weak recommendation based on low or very low quality evidence. It is important to note that for ASFA category IV indications, this grading system would imply that ASFA category IV indication with Grade 1A is a strong recommendation against the use of TA supported by high quality evidence.

E The ASFA category is listed for each therapeutic apheresis modality discussed. Some categories have additional information provided in the condition column to further specify a subgroup of patients for whom the category was assigned. It is important to recognize that only in this particular subset of patients an ASFA category was assigned. More information is available in the text of the

Fig 1. (*Continued*)

F 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 often less important than the quality of the scientific reports. Considering numbers alone can be misleading as negative results tend to be published less frequently.

G This section is used when there are several different TA procedures used and it was necessary to subdivide available scientific reports; as well as in the situation when different subset of patients are being analyzed. Not all entries will have this section.

H 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 four 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).

I 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.

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

K Case report (CR). Number of case reports (with total number of patients reported). If there were more than 50 case reports or there is a significant number of larger studies either >50 or NA (not applicable) was used, respectively.

L A brief description of the disease is provided here. Typically, this entry contains information on clinical signs and symptoms, pathophysiology, typical presentation and the severity of the disease.

M This section provides brief description of therapeutic modalities available to treat the disease. The committee attempted to cover all reasonable modalities (e.g., medications, surgical procedures, etc.); however, this section is not intended to provide extensive discussion of any treatment modality. In addition, for some entities the management of standard therapy failure is discussed (e.g., steroids), especially when the failure of established therapies may trigger the use of therapeutic apheresis.

N This section discusses a rationale for therapeutic apheresis as well as supporting evidence of its use. Most important reports are briefly discussed here. The effort was made to discuss a rationale for TA in the context of the current understanding of pathophysiology.

O 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 a positive clinical outcome. Not all diseases have specific technical notes; in such instances a general statement referring to the introductory text is provided.

P This section specifies commonly used volumes of plasma or blood treated. Typically this value for plasma exchange is between 1 and 1.5 total plasma volumes (TPV).

Q The proposed frequency of treatment is listed here. The frequency is based on the data from published reports however, due to variability of such reports; the committee suggested what is believed to be the clinically most appropriate frequency. Application of this information may vary depending on the patient and clinical presentation, and is left to the treating physician.

R The type of replacement fluid most frequently used is listed here. Terms such as plasma or albumin were used to denote the type of replacement fluid. No attempt was made to include all possible variations (e.g., 4 vs. 5% albumin; fresh frozen plasma vs. thawed plasma). In addition, blood component modifications are listed here, if relevant (e.g., RBC modifications for red cell exchange). "NA" is used when there is no replacement fluid necessary (e.g. extracorporeal photopheresis).

S This section provides basic criteria for discontinuation of apheresis procedures (i.e., end points/outcomes, both clinical and laboratory). In some instances numbers of procedures/series which may be reasonably employed in the particular clinical situation, is suggested based upon available data. The committee believed that a thoughtful approach to patient management is required to establish reasonable and scientifically sound criteria for discontinuation of treatment. This section does not replace the need for conversation between treating and apheresis physicians.

T A number of references are cited for each fact sheet. Additional information may be obtained after perusing the cited references. All references are combined and printed at the end of this document.

U The terms used to identify most relevant articles are listed here.

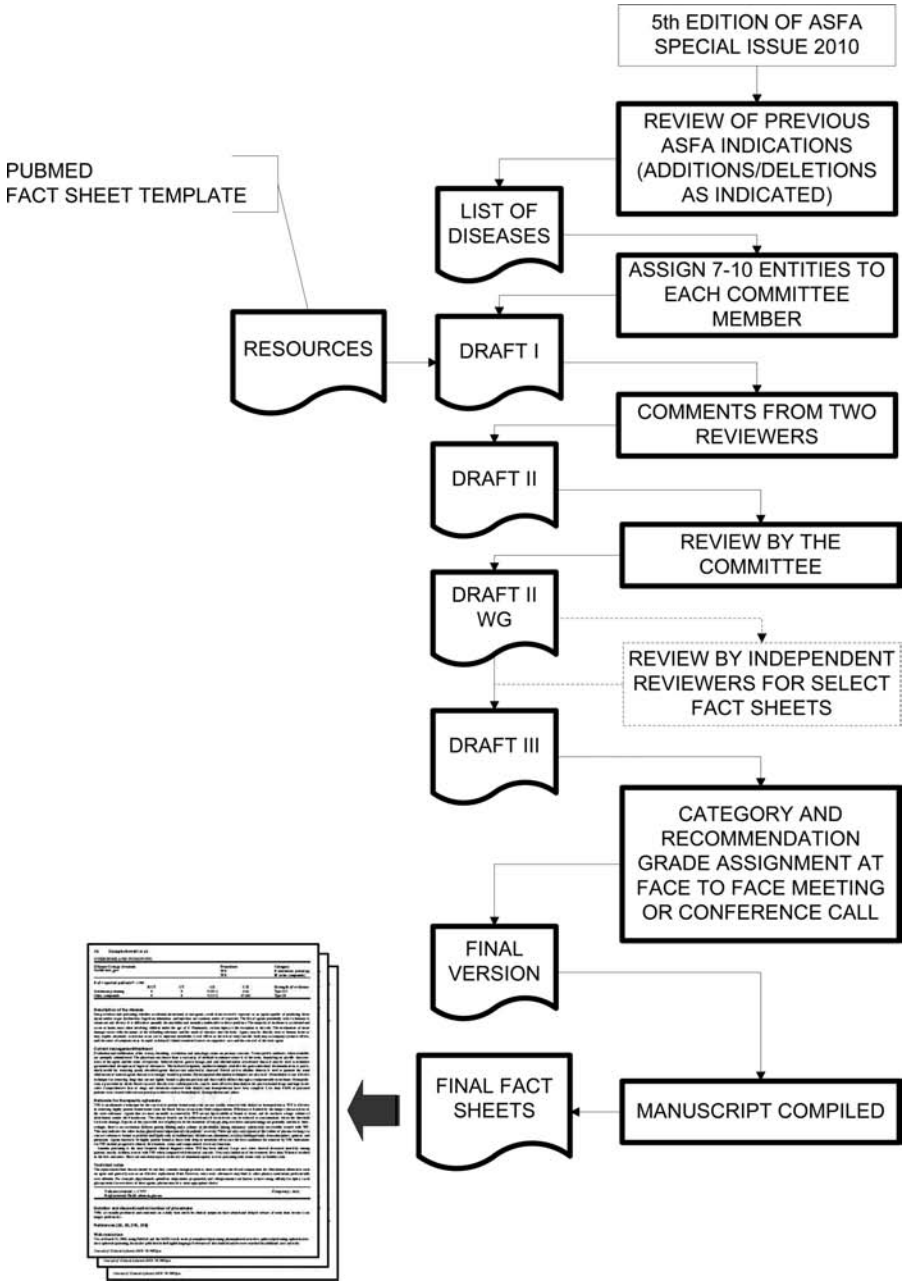

Fig. 2. Systematic approach to ASFA category assignment, recommendation grade and ASFA Fact Sheet generations and revisions used in the ASFA Special Issue 2013.

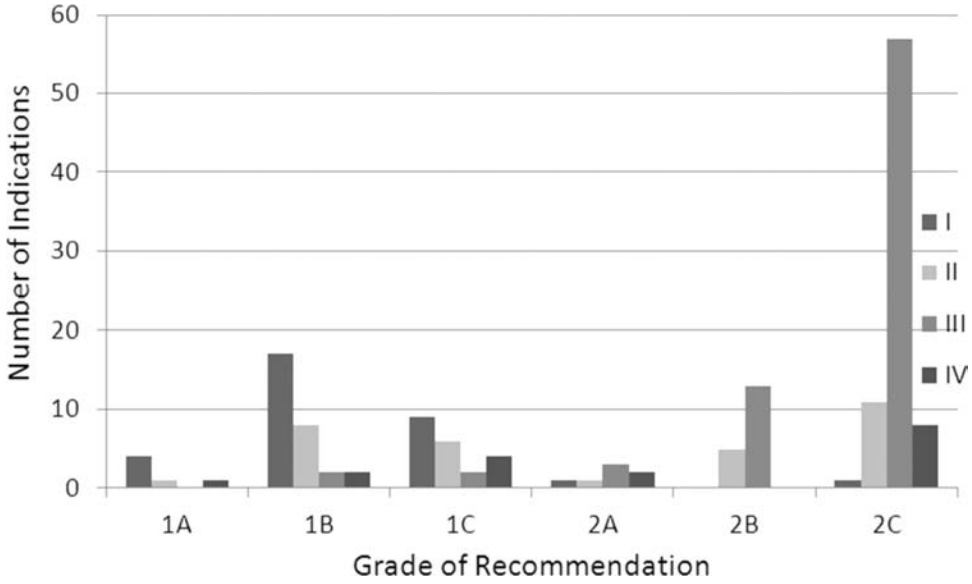

Fig. 3. The ASFA Category I–IV Indications and the Recommendation Grade in the ASFA Special Issue 2013.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

Incidence: 0.4–0.9/100,000/yr[+]	**Procedure**	**Recommendation**	**Category**
	TPE	Grade 2C	II
# of reported patients*: <100			
RCT	**CT**	**CS**	CR
0	0	5(30)	17(22)

[+]In pediatric population; in adult patients, incidence studies are not available.

Description of the disease

Acute disseminated encephalomyelitis (ADEM) is an acute inflammatory monophasic demyelinating disease that predominantly affects the white matter of the brain and spinal cord, which typically occurs after a viral or bacterial infection or vaccination. The pathogenesis is thought to be disseminated multifocal inflammation and patchy demyelination associated with transient autoimmune response against myelin or other autoantigens. Viral or bacterial epitopes resembling myelin antivgens have the capacity to activate myelin reactive T cell clones through molecular mimicry, and thus can elicit a CNS-specific autoimmune response. Alternatively, the viral or bacterial superantigens could activate existing myelin autoreactive T cells clones through a nonspecific inflammatory process. ADEM typically begins within days to weeks following the antigenic challenge. The typical presentation is that of an acute encephalopathy (change in mental status) accompanied by multifocal neurological deficits (ataxia, weakness, dysarthria, and dysphagia). It is usually a monophasic illness that lasts from 2–4 weeks. However, recurrent or multiphasic forms have been reported. Children and young adults are predominantly affected. The mortality rate is around 5%, with complete recovery in 50–75% of cases.

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 (MS) 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 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

Once ADEM is diagnosed, the therapeutic aim is to abbreviate the CNS inflammatory reaction as quickly as possible, and to speed up clinical recovery. There have been no randomized controlled trials for the treatment of ADEM, and treatments are based on the analogy of the pathogenesis of ADEM with that of MS. High-dose intravenous corticosteroids, such as methylprednisolone 1 g/day for 3–5 days are considered as first-line therapy. It might be followed by a prolonged oral prednisolone taper of 3–6 weeks. Corticosteroids are considered effective because of their anti-inflammatory and immunomodulatory effects with additional beneficial effect on cerebral edema. Corticosteroids hasten recovery and result in clinical improvement in up to 60% of patients. TPE should be considered for patients with severe ADEM, who respond poorly to steroid treatment or in whom it is contraindicated. Additionally, IVIG is also used and is reserved for patients who do not respond to corticosteroids.

Rationale for therapeutic apheresis

TPE 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 autoantibodies as well as through immunomodulation. In the acute phase of ADEM, cytokines such as tumor necrosis factor, soluble tumor necrosis factor receptor 1, IL-6 and IL-10 are elevated. Antibodies to gangliosides, such as GM1 and CD1a, and myelin basic protein-reactive T-helper 2 cells, may be present, which can be removed by TPE. In a recent study, early initiation of TPE (within 15 days of onset) in acute attacks of CNS demyelination (including 7 cases of ADEM) was identified as a predictor of clinical improvement at 6 months.

Technical notes

Volume treated: 1–1.5 TPV **Frequency**: Every other day
Replacement fluid: Albumin

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. In the largest case study, TPE achieved moderate and marked sustained improvement in 50% of the patients. Factors associated with improvement were male sex, preserved reflexes and early initiation of treatment. In most published literature, response was noticeable within days, usually after 2–3 exchanges. If improvement is not observed early in treatment, then it is unlikely a response will occur. TPE therapy consists of 3–6 treatments, most commonly 5.

References [11–24]

*As of February 16, 2012 using PubMed and the MeSH search terms acute disseminated encephalomyelitis, plasmapheresis, plasma exchange for articles published in the English language. References of the identified articles were searched for additional cases and trials.

ACUTE INFLAMMATORY DEMYELINATING POLYNEUROPATHY (GUILLAIN-BARRÉ SYNDROME)

Incidence: 1–2/100,000/yr	**Condition**	**Procedure**	**Recommendation**	**Category**
		TPE	Grade 1A	I
	After IVIG^{+}	TPE	Grade 2C	III

# of reported patients*: >300				
	RCT	**CT**	**CS**	**CR**
	19(1770)	0	9 (369)	10 (11)
After IVIG^{+}	0	0	1(46)	NA

$^{+}$Completed course of IVIG at 2 g/kg.

Description of the disease

Acute Inflammatory Demyelinating Polyneuropathy (AIDP; Guillain-Barré Syndrome [GBS]) 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. Weakness progresses over a period of 12 h to 28 days before the nadir is reached and 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 opthalmoplegia, ataxia, and areflexia. AIDP is distinguished from CIDP which is a chronic disorder (see fact sheet on CIDP). An autoimmune pathogenesis is strongly suggested due to the presence of antibodies against four gangliosides GM1, GD1a, GT1a, and GQ1b which differ by the number and position of sialic acids (M, D, T and Q represent mono-, di-, tri- and quadric sialosyl groups) in the majority of patients as well as in animal models of the disease. Observations of preceding infectious illness, such as Campylobacter, suggest cross-reactive antibodies may be a component in disease pathogenesis. There are several scales to evaluate severity and prognosis of the disease (e.g., GBS disability score, Medical Research Council sum score, Erasmus GBS Respiratory Insufficiency Score and Erasmus GBS Outcome Score). The GBS disability score (used by some payers): 0, A healthy state; 1, Minor symptoms and capable of running; 2, Able to walk 10 m or more without assistance but unable to run; 3, Able to walk 10 m across an open space with help; 4, Bedridden or chair bound; 5, Requiring assisted ventilation for at least part of the day; and 6, Dead.

Current management/treatment

Since spontaneous recovery is anticipated in most patients, supportive care is the mainstay of treatment in ambulatory patients with AIDP. Severely affected patients may require intensive care, mechanical ventilation, and assistance through the paralysis and necessary rehabilitation over several months to a year or more. Corticosteroids when used alone show minimal, if any, therapeutic effect. TPE was the first therapeutic modality to impact the disease favorably and several major randomized controlled clinical trials have confirmed its efficacy. An international randomized trial compared TPE, IVIG and TPE followed by intravenous immunoglobulin (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). Other therapeutic modalities studied include immunoadsorption apheresis, CSF filtration, and double filtration plasmapheresis (DFPP). Since IVIG is readily available and has a higher rate of treatment completion, it is frequently used as initial therapy; the typical dose is 0.4 g/kg for 5 consecutive days.

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 vs. 31 days for TPE compared to control, respectively. In the North American Trial the median time to walk without assistance was 53 days vs. 85 days. The Cochrane Neuromuscular Disease Group review of TPE in AIDP performed in 2012 found that TPE is most effective when initiated within 7 days of disease onset. It was further concluded that TPE has beneficial effect in severely and mildly affected individuals; with significantly increased proportion of patients able to walk after four weeks. Interestingly, there was increased number of patients who relapsed after TPE than in the control group, but one year outcomes showed greater proportion of patients with increased muscle strength and decreased risk of severe muscle sequelae in TPE group. Another Cochrane Database Systematic Review noted that IVIG treatment in AIDP is more likely to be completed, but does not offer increased therapeutic benefit in comparison to TPE. American Academy of Neurology reports equal strength of evidence to support the use of TPE or IVIG in the treatment of AIDP. However, Winters et al noted that the cost of IVIG treatment in GBS is twice high as the cost of TPE with equivalent clinical response.

Technical notes

The typical TPE strategy is to exchange 200–250 mL plasma per kg body weight over 10–14 days. This will generally require 5–6 one volume TPE procedures with 5% albumin replacement. Plasma is not routinely used for replacement. Since autonomic dysfunction may be present, affected patients may be more susceptible to volume shifts, blood pressure and heart rate changes during extracorporeal treatment. Relapses may occur in approximately 10% of patients 2–3 weeks following either treatment with TPE or IVIG. When relapses occur, 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. Frequently, when patients do not respond to IVIG, TPE is requested as the secondary therapy. Retrospective studies showed that such approach has limited therapeutic benefit, yet it is significantly more expensive. Requests for TPE after IVIG treatment should be only considered in the context of each patient's clinical situation.

Volume treated: 1–1.5 TPV **Frequency:** Every other day
Replacement fluid: Albumin

Duration and discontinuation/number of procedures

Five to six TPE over 10–14 days are recommended, see technical notes above for details.

References [12, 25–49]

*As of October 1, 2012 using PubMed and the MeSH search terms acute inflammatory demyelinating polyradiculoneuropathy or Guillain Barre and plasmapheresis, plasma exchange, or apheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

ACUTE LIVER FAILURE

Incidence: Exact incidence unknown. Number of liver transplants are >6,000/ yr (US)	**Procedure** TPE	**Recommendation** Grade 2B	**Category** III

# of reported patients*: >300

RCT	**CT**	**CS**	**CR**
1 (120)	0	37 (838)	51 (69)

Description of the disease

Acute liver failure (ALF) can develop in a normal liver (known as fulminant hepatic failure [FHF]) or in the setting of chronic liver disease. The top two causes of ALF are viral hepatitis and acetaminophen toxicity. Other causes include ingestion of hepatotoxins/other drugs, autoimmune hepatitis and Wilson's disease (see fact sheet on Wilson's disease). The mortality rate in FHF is 50–90% due to acute metabolic disturbances, hepatic encephalopathy and severe coagulopathy; however, following liver transplantation, survival rates improve. 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 a recovery rate less than 20%. 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. Generally ABO identical transplantations are performed except in limited circumstances (see fact sheet on liver transplantation, ABO incompatible). Deceased donor transplantation is considered first-line therapy for acute liver failure in Europe and the US, while in Japan, artificial liver support, consisting of plasma exchange and hemofiltration, is more aggressively used in patients with fulminant hepatitis.

Current management/treatment

Currently there are no FDA approved cell-based liver support systems available in the US and 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 noncell-based therapies include: TPE, albumin dialysis, MARS (Molecular Adsorbents Recirculation System; in the US, the MARS system is cleared for use in the treatment of drug overdose and poisonings only), Fractionated plasma separation and adsorption (FPSA), 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 plasma, prothrombin complex concentrate, recombinant factor VIIa and cryoprecipitate and conventional continuous veno-venous hemofiltration. A recent randomized control trial in ALF patients with hepatic encephalopathy showed that both MARS and TPE + MARS therapy are equivalent with regard to clinical outcome (30-day mortality). However, TPE + MARS therapy reduced serum total bilirubin level more effectively and was more cost-effective.

Rationale for therapeutic apheresis

In FHF, TPE can remove albumin bound toxins as well as 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, and decreased systemic vascular resistance and cerebral blood flow. Several studies show improved cerebral blood flow, mean arterial pressure, cerebral perfusion pressure, cerebral metabolic rate, increased hepatic blood flow, and improvements in other laboratory parameters such as cholinesterase activity or galactose elimination capacity. Despite these seemingly positive changes in physiological parameters, its impact on clinical improvement is still unclear. TPE may also restore hemostasis by providing coagulation factors and removing activated clotting factors, tissue plasminogen activator, fibrin and fibrinogen degradation products. In some patients, the liver may recover during TPE and in other patients, failure may persist necessitating liver transplantation. Aggressive TPE has been used as a bridge to liver transplantation. In intractable pruritus, TPE is thought to remove bile acids. Charcoal hemoperfusion has previously been used by some groups for this indication, but this is no longer available in the US. In a recent large case series, TPE was shown to decrease cytokine levels (IFN-γ, IL-10, IL-4, IL-2, and TNF-α) which are generally seen as important for the systemic inflammatory state in these patients.

Technical notes

Since plasma has citrate as an anticoagulant and there is significant hepatic dysfunction, whole blood: ACD-A ratio should be adjusted accordingly to prevent severe hypocalcemia in ALF. Simultaneous calcium infusion can be used if necessary. Patient should also be monitored for development of metabolic alkalosis. Some groups have performed simultaneous hemodialysis to mitigate this adverse event. There is a preference for plasma as a replacement fluid due to moderate to severe coagulopathy; however, addition of albumin is acceptable. Calcium supplementation should be strongly considered.

Volume treated: 1–1.5 TPV **Frequency:** Daily
Replacement fluid: Plasma, albumin

Duration and discontinuation/number of procedures

In ALF, daily TPE is performed until transplantation or self-regeneration occurs. The biochemical response to TPE should be evaluated in laboratory values drawn the following day (>12 h or more after TPE). Samples drawn immediately after completion of the exchange would be expected to appear better compared to pre-exchange levels. Rarely TPE can be performed 2–3 times per week for 4 weeks in primary biliary cirrhosis to alleviate pruritus until a clinical response is observed.

References [50–70]

*As of September 21, 2012 using PubMed and the MeSH search terms acute hepatic/liver failure, fulminant liver/hepatic failure and plasmapheresis, plasma exchange for articles published in the English language. References of the identified articles were searched for additional cases and trials.

AGE RELATED MACULAR DEGENERATION, DRY

Incidence: 1.8/100,000/yr	**Procedure**	**Recommendation**	**Category**
	Rheopheresis	Grade 1B	I

# of reported patients*: >300

RCT	**CT**	**CS**	**CR**
5 (295)	2(371)	8 (101)	1(1)

Description of the disease

Age-related macular degeneration (AMD) is the leading cause of blindness in the West in those over 60 years old. It is a progressive condition of the macula with central vision loss affecting reading, facial recognition, and driving. AMD is characterized by debris collection (drusen) beneath the retinal pigment epithelium (RPE). This initial stage is ''dry AMD.'' Over 10 years, 12.5% progress to ''wet AMD", with growth of blood vessels into the choroid (choroidial neovascularization). Risk factors for AMD include smoking, hypertension, and elevated body mass index. There are direct correlations with cholesterol, fibrinogen, and α2-macroglobulin levels. Mutations in complement regulatory genes are also associated including mutations in Complement Factor H (CHF), LOC387715, and Complement Factor B. It is estimated that the HF1 CHF mutation, LOC387715 mutation, and smoking account for 61% of the attributable risk for AMD.

The pathogenesis of AMD has not been completely elucidated. There appears to be a role for inflammation, age related changes in blood flow and changes in blood rheology. 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. The resulting hypoxia leads to a loss of the ability of the RPE to phagocytize cellular debris generated by normal turnover and possible RPE injury leading to the recruitment of dendritic cells. These cells, in turn, may contribute to the deposition of extracellular debris, complement fragments, and membrane attack complex producing drusen. The deposits lead to an increase in the oxygen diffusion distance, worsening hypoxia and greater RPE dysfunction/injury. Increasing hypoxia leads to vascular growth factor production resulting in blood vessel in-growth and wet AMD.

Current management/treatment

Dry AMD treatment is limited to high dose supplementation of vitamins C and E, beta carotene, and zinc. Wet AMD is treated 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 rheopheresis (also called DFPP, cascade filtration plasmapheresis, or double membrane plasmapheresis) is that high-molecular weight molecules that have been associated with risk of AMD development (e.g., fibrinogen, LDL-cholesterol, fibronectin, von Willebrand factor [VWF]) 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.

Case series, two controlled trials, and five completed randomized controlled trials have reported efficacy of rheopheresis in treating dry 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 viscosity parameters, shortening of arteriovenous passage time, and improvement on electroretinogram. The studies have shown improvement shortly after treatment completion that lasted up to four years. The Utah trial (*Swartz*) randomized 30 patients to three arms (treatment (rheopheresis), placebo, and no treatment) and demonstrated improvement in the Pepper Visual Skills for reading test scores of +27% for the treatment arm but declines of −18 and −20% for the other arms. The MAC trial (*Brunner*) randomized 40 patients to treatment versus no treatment. Visual acuity in the treatment group improved by 0.63 lines on the ETDRS chart while the control decreased by 0.94 lines. The results of the MIRA-1 trial (*Pulido*), a large randomized double-blinded placebo (sham procedure) controlled trial that enrolled 216 patients, failed to demonstrate a significant difference between controls and treatment groups due to the controls doing better than predicted. Analysis revealed that 37% of treated patients and 29% of control patients were protocol violators who did not fulfill the trial's inclusion criteria of AMD leading to bias in the study's final outcome. Excluding those subjects who had vision loss due to other causes, this trial demonstrated significant improvement with treatment but the trial was under-powered for FDA licensure. The Dry AMD Treatment with Rheopheresis Trial (*Koss*) randomized 43 patients. The trial demonstrated an increase in best corrected visual acuity of 0.95 visual acuity lines on ETDRS charts in the treated group compared to the controls. Nine percent of treated patients demonstrated an increase in 2 or more visual acuity lines and none demonstrated a worsening of vision. No control patients demonstrated improvement of this magnitude while 24% demonstrated visual acuity loss. The most recent trial (*Rencova*) randomized 32 patients. At 1.5-year follow-up, stabilization or improvement of visual acuity occurred in 72% of treated patients and 39% of controls. The largest controlled trial to date is from the Rheo-Net registry (*Klingel*). Two hundred seventy nine patients with dry AMD were treated and compared to 55 untreated controls. In the treated group, visual acuity gain greater than or equal to one ETDRS line was seen in 42% compared to such improvement in 26% of controls. Vision loss greater than or equal to one ETDRS line was seen in 17% of the treated patients vs. 40% of controls. These were statistically significant differences.

Technical notes

The majority of series and trials used DFPP. In this, plasma is separated by 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. These devices are not available in the United States. One case series did indicate that TPE 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 DFPP) and the authors provide inadequate information to determine whether there was a benefit with TPE.

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.

Volume treated: 0.8–1.2 TPV **Frequency:** 8–10 treatments (two per week) over 8–21 weeks
Replacement fluid: NA

Duration and discontinuation/number of procedures

Efficacy of a single course 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.

Currently, the devices necessary for this treatment are not licensed in the United States but are available in Europe and Canada.

References [71–94]

*As of October 21, 2012 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. This fact sheet includes abstracts in the summary of published reports and considers them in determining the recommendation grade and category.

AMYLOIDOSIS, SYSTEMIC

Incidence: Primary AL amyloidosis: 6–10/1,000,000/year; DRA: Unknown but uncommon with current high-flux dialysis membranes; AA amyloidosis: Prevalence of 0.5% with inflammatory rheumatologic disorders and 10–20% with FMF	**Procedure**	**Recommendation**	**Category**
	TPE	Grade 2C	IV

# of reported patients*: <100			
RCT	**CT**	**CS**	CR
0	0	4 (5)	3 (3)

AA amyloidosis = serum amyloid A protein; AL amyloidosis = monoclonal immunoglobulin light chain; DRA = dialysis-related amyloidosis; FMF = familial Mediterranean fever

Description of the disease

Amyloidosis refers to a number of genetic and acquired disorders characterized by pathological extracellular precipitation of insoluble polymeric fibrils consisting of aberrant proteins or protein precursors, and leading to progressive organ damage. The familial disorders are rare and predominantly autosomal dominant, arising from missense mutations that lead to deposition of precursor proteins in kidneys, nerves and cardiac tissues. The most common acquired disorders involve deposition of monoclonal immunoglobulin light chain (AL amyloidosis), serum amyloid A protein (AA amyloidosis) or beta 2-microglobulin (dialysis-related amyloidosis [DRA]). AL amyloidosis, associated with multiple myeloma, Waldenström macroglobulinemia, non-Hodgkin lymphoma, or as a primary plasma cell dyscrasia, can affect the skin, nerves, kidneys, liver, heart, tongue, muscles and coagulation system. Acquired factor X deficiency, acquired von Willebrand syndrome, coagulopathy due to liver failure and/or vascular fragility are responsible for the bleeding diathesis affecting roughly one-quarter of patients with AL amyloidosis. AA amyloidosis, associated with chronic infection, malignancies or inflammation (including rheumatoid arthritis, juvenile rheumatoid arthritis and hereditary periodic fever syndromes, including familial Mediterranean fever [FMF]), predominantly affects the kidneys, leading to nephrotic syndrome and renal failure. DRA primarily affects bones, joints and soft tissues. The diagnosis of AA and AL amyloidosis requires biopsy of affected tissues or abdominal fat, identification of amyloid deposits with typical Congo red staining characteristics and immunostaining to define the specific abnormal protein. DRA can be diagnosed by characteristic radiographic bony changes; however, histologic confirmation is recommended.

Current management/treatment

Approaches to therapy involve reducing protein precursor production, preventing aggregation, or inducing resorption. Primary systemic AL amyloidosis is treated with the same chemotherapy regimens, targeted agents and autologous stem cell transplantation approaches that are used for myeloma. End-organ complications are managed with symptomatic and supportive care. Management of coagulopathy with AL amyloidosis includes infusion of plasma, cryoprecipitate, recombinant factor VIIa and/or bypass factors. Chemotherapy and splenectomy have also been anecdotally beneficial. AA amyloidosis is managed by aggressively treating the underlying inflammatory disorder. Colchicine is an effective agent to control the periodic fevers and tissue complications, including AA amyloidosis, due to FMF. Immunomodulatory and anti-cytokine regimens may also be beneficial for certain inflammatory disorders that lead to AA amyloidosis. DRA is managed with aggressive dialysis using membranes and treatment protocols that optimize clearance of beta 2-microglobulin. Bone and joint complications of DRA are managed symptomatically. No agents are yet approved that directly solubilize the amyloid deposits that deposit in affected tissues.

Rationale for therapeutic apheresis

Case reports and small case series have described the use of specialized adsorption columns or membrane filters to remove beta 2-microglobulin with DRA, and intensive TPE with immunosuppressive treatment to manage rapidly progressive glomerulonephritis (RPGN) with AA amyloidosis. In one report, regular TPE treatments over 8 months combined with melphalan and prednisone improved macroglossia and skin lesions and significantly reduced serum interleukin-6 levels in a patient with AL amyloidosis; however, the relative benefits of the drugs versus apheresis was not discernible. TPE was used in combination with hemodialysis in two patients with AL amyloidosis and renal failure, one of whom had amyloid arthropathy. Although this study confirmed feasibility of performing these procedures in tandem, there was no reported objective benefit for the underlying disease processes. One case report described a transient, modest improvement in coagulation parameters with AL amyloidosis and factor X deficiency after 2 L TPE procedures with plasma replacement. However, another report using a similar approach was ineffective in correcting AL amyloid associated severe factor X deficiency. No data exist supporting the use of TPE for neuropathy or other complications associated with AL amyloidosis, DRA or AA amyloidosis.

References [95–101]

*As of July 3, 2012 using PubMed and the MeSH search terms Systemic amyloidosis, amyloidosis, light chain amyloidosis, plasmapheresis, plasma exchange, apheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

AMYOTROPHIC LATERAL SCLEROSIS

Incidence: 2–5/100,000 (new cases each year)	**Procedure** TPE	**Recommendation** Grade 1C	**Category** IV
# of reported patients <100			
RCT	**CT**	**CS**	**CR**
0	1 (7)	2(8)	0

Description of the disease

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease or motor neuron disease, is a relentlessly progressive disease associated with destruction and dysfunction of neurons in the brain and spinal cord that control voluntary muscles that are used for movement (upper and lower motor neurons). It affects motor function, leaving the sensation and cognitive ability intact. Symptoms include progressive muscle weakness, atrophy, fasciculations and spasticity eventually leading to paralysis that may extend to muscles used for swallowing and breathing. The cause of ALS is largely unknown and it is unclear why it affects some patients and not others. Some preliminary work from the National Institute of Neurological Disorders and Stroke (NINDS) showed some mutations in the gene that produces the antioxidant enzyme SOD1 were associated with some cases of familial ALS. This SOD1 mutation has also been shown in animal models to be associated with motor neuron degeneration and contributes to this theory of causation.

Current management/treatment

Riluzole (Rilutek) has been approved by the FDA to slow progression of ALS and improve survival by possibly several months. This drug does not reverse the disease or reinstate lost function. It can be hepatotoxic in up to 10% of patients.

Rationale for therapeutic apheresis

Multiple small series and a small controlled trial in the late 1970s and early 1980s failed to show any benefit for TPE alone or TPE in combination with immunosuppressive therapy for patients with ALS.

References [102–104]

*As of October 14, 2012 using PubMed and the MeSH search terms Amyotrophic lateral sclerosis and plasmapheresis, plasma exchange.

ANCA-ASSOCIATED RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (GRANULOMATOSIS WITH POLYANGIITIS; WEGENER'S GRANULOMATOSIS)

Incidence: 8.5/1,000,000/yr	**Condition**	**Procedure**	**Recommendation**	**Category**
	Dialysis dependence[+]	TPE	Grade 1A	I
	DAH	TPE	Grade 1C	I
	Dialysis independence[+]	TPE	Grade 2C	III

# of reported patients*: >300

RCT	**CT**	**CS**	**CR**
8 (296)	1 (26)	22 (347)	NA

[+] At presentation, defined as Cr>6 mg/dL. DAH = diffuse alveolar hemorrhage.

Description of the disease

ANCA-associated RPGN is one cause of the clinicopathologic entity, RPGN. RPGN consists of rapid loss of renal function with the histologic finding of crescent formation in over 50% of glomeruli. These crescents represent a proliferation of cells within Bowman's space of the glomerulus due to the extravasation of proteins into this space. These cells consist of proliferating parietal epithelial cells as well as infiltrating macrophages and monocytes.

RPGN is NOT A SINGLE DISEASE ENTITY but is a clinical syndrome that can result from a number of etiologies. Histologic classification divides RPGN into three subtypes based on the immunofluorescence pattern on renal biopsy. These categories are:

1. Linear deposits of IgG due to autoantibodies to type IV collagen representing anti-glomerular basement membrane GN (anti-GBM). It accounts for 15% of cases (see fact sheet on anti GBM disease).
2. Granular deposits of immune complexes caused by a variety of GNs including post-streptococcal GN, Henoch-Schönlein purpura, IgA nephropathy, membranoproliferative GN, cryoglobulinemia, and lupus nephritis. Immune-complex RPGN accounts for 24% of cases of RPGN (see fact sheets on immune-complex RPGN, Henoch-Schönlein purpura, and IgA nephropathy).
3. Minimal immune deposits in the glomerulus with the presence of anti-neutrophil antibodies [either C-ANCA (cytoplasmic) or P-ANCA (perinuclear)] in the serum. This pauci-immune RPGN, also referred to as ANCA-associated RPGN, is seen in granulomatosis with polyangiitis, abbreviated GPA (Wegener's granulomatosus) and microscopic polyangiitis (MPA). GPA and MPA are related systemic vasculitidies, with ANCA positivity and similar outcomes. The majority of patients who present with RPGN are ANCA positive and are therefore in this category. C-ANCA is more often associated with GPA, and P-ANCA with MPA.

It is important to identify the specific category of RPGN present in their patient as TPE treatment protocols and responses differ. This sheet discusses ONLY ANCA-associated RPGN. ANCA-associated small vessel vasculitis encompasses a clinical spectrum of disease which ranges from renal-limited vasculitis to systemic involvement, including MPA, GPA, 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). When ANCA and anti-GBM antibody are both present, the disease should be considered to represent anti-GBM disease (see fact sheet on anti-glomerular basement antibody disease). Diffuse alveolar hemorrhage (DAH) associated with ANCA vasculitis poses significant risk of mortality.

Current management/treatment

Without treatment, GPA and MPA progress to organ failure including end-stage renal disease (ESRD) over months. A number of immunosuppressive protocols have been used. The current standard approach to management of ANCA small vessel vasculitis is combination therapy consisting of high-dose corticosteroids and cytotoxic immunosuppressive drugs. Cyclophosphamide and rituximab have been proven clinically effective. Two randomized trials indicate that rituximab is an effective alternative to cyclophosphamide in new or relapsing patients. Other drugs that have been used include leflunomide, deoxyspergualin, tumor necrosis factor blockers, calcineurin inhibitors and antibodies against T-cells. Overall, existing controlled trials in GPA and MPA suggest no benefit of TPE for many cases. Important exceptions are: Patients with (1) severe active kidney disease, that is, requiring dialysis therapy or with serum creatinine concentration above 6 mg/dL; (2) severe pulmonary hemorrhage; and (3) anti-GBM disease who are also ANCA-positive.

Rationale for therapeutic apheresis

ANCA have high molecular weights, low volume of distribution, low turnover rates and a long half-life, and are likely pathogenic in pauci-immune RPGN. The presence of ANCA indicates a humoral component to disease pathogenesis. TPE has been added in life-threatening cases, such as ANCA with DAH, and also in patients who are dialysis-dependent (or for whom initiation of dialysis is imminent). 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, 3 prospective controlled trials consisting of a total 87 patients, found no benefit of TPE over standard therapy. Later subset analysis in 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.

The role of TPE in GPA/MPA patients with advanced kidney impairment was addressed in MEPEX trial by the European Vasculitis Study Group. In this study of 137 patients presenting with ANCA-associated vasculitis with a serum creatinine >5.7 mg/dL, patients received standard therapy of oral corticosteroids and cyclophosphamide and were randomly assigned adjunctive therapy of either TPE or pulse methylprednisolone (1000 mg/d × 3 days). Mean baseline serum creatinine was 8.3 mg/dL, and 69% required dialysis. Randomization to the treatment arm which included TPE (7 treatments over 14 days) was predictive of dialysis independence at 12 months (54% compared to 29%). The addition of TPE was associated with a 24% risk reduction for progression to ESRD at one year. TPE was also a positive predictor for those already dialysis-dependent. High mortality (roughly 25%) in both groups at one year remained a concern. MEPEX was the largest study in a subsequent meta-analysis of 387 patients from nine trials, with creatinine levels ranging from 3.2 to 13.5 mg/dL. The addition of TPE to standard immunosuppression was associated with reduced risk of ESRD or death. A multicenter international RCT is in progress to establish the efficacy of TPE in additional to immunosuppressive therapy and glucocorticoids at reducing death and ESRD in ANCA positive vasculitis (PEXIVAS; ClinicalTrials.gov registration number NCT00987389).

Randomized controlled trials of TPE in patients with RPGN and pulmonary hemorrhage have not been conducted. However, a retrospective case series reported effective management of pulmonary hemorrhage in ANCA vasculitis.

Technical notes

In patients with pulmonary hemorrhage, replacement with plasma is recommended to avoid dilutional coagulopathy resulting from nonplasma 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 6–9 procedures.

References [105–127]

*As of October 10, 2012 using PubMed and the MeSH search terms ANCA or antineutrophil cytoplasmic antibody and plasmapheresis or plasma exchange for articles published in the English language. References of the identified articles were searched for additional cases and trials.

ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE (GOODPASTURE'S SYNDROME)

Incidence: <1/100,000/yr	**Condition**	**Procedure**	**Recommendation**	**Category**
	Dialysis-dependent^{+}; no DAH	TPE	Grade 2B	III
	DAH	TPE	Grade 1C	I
	Dialysis-independent^{+}	TPE	Grade 1B	I

# of reported patients*: >300

RCT	**CT**	**CS**	**CR**
1 (17)	0	17 (430)	19

$^{+}$At presentation, defined as Cr> 6 mg/dL. DAH = diffuse alveolar hemorrhage

Description of the disease

Anti-GBM disease is one cause of the clinicopathologic entity, RPGN. RPGN consists of rapid loss of renal function with the histologic finding of crescent formation in over 50% of glomeruli. These crescents represent a proliferation of cells within Bowman's space of the glomerulus due to the extravasation of proteins into this space. These cells consist of proliferating parietal epithelial cells as well as infiltrating macrophages and monocytes.

RPGN is NOT A SINGLE DISEASE ENTITY but is a clinical syndrome that can result from a number of etiologies. RPGN is divided into three categories based on the immunoflourescence pattern on renal biopsy. These categories are:

1. Linear deposits of IgG due to autoantibodies to type IV collagen representing anti-GBM GN. It accounts for 15% of cases.
2. Granular deposits of immune complexes caused by a variety of GNs including post-streptococcal GN, Henoch-Schönlein purpura, IgA nephropathy, membranoproliferative GN, cryoglobulinemia, and lupus nephritis. Immune-complex RPGN accounts for 24% of cases of RPGN (see fact sheets on immune-complex RPGN, Henoch-Schönlein purpura, and IgA nephropathy).
3. Minimal immune deposits in the glomerulus with the presence of anti-neutrophil antibodies [either C-ANCA (cytoplasmic) or P-ANCA (perinuclear)] in the serum. This pauci-immune RPGN, also referred to as ANCA-associated RPGN, is seen in granulomatosis with polyangiitis, abbreviated GPA (Wegener's) and microscopic polyangiitis (MPA). GPA and MPA are related systemic vasculitidies, with ANCA positivity and similar outcomes. The majority of patients who present with RPGN are ANCA positive and are therefore in this category. C-ANCA is more often associated with GPA, and P-ANCA with MPA.

It is important to identify the specific category of RPGN present in their patient as TPE treatment protocols and responses differ. Clinically, anti-GBM is typically a pulmonary-renal syndrome, consisting of RPGN and often DAH. Up to 30–40% of patients have been reported to have renal limited involvement (no DAH). Pulmonary symptoms range from breathlessness to overt hemoptysis. Chest radiography is a useful tool in demonstrating DAH but the findings are nonspecific. Anti-GBM is associated with a specific HLA allele, DRB1*1501. DAH is associated with exposure to hydrocarbons, chemical compounds, cocaine, marijuana, hard metal dust, fire smoke, and cigarette smoking. Almost all patients have anti-GBM antibodies detectable in their blood. This antibody is directed toward the noncollagenous 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-associated RPGN in the short-term but more like ANCA-associated RPGN in the long-term.

Current management/treatment

In anti-GBM, treatment includes the combination of TPE, cyclophosphamide, and corticosteroids. In general, the disease does not relapse in a successfully treated patient and patients do not require chronic immunosuppression. The exception is patients who have ANCA in addition to anti-GBM antibodies. These patients respond rapidly to treatment, like anti-GBM, but can relapse, like ANCA-associated RPGN. These patients require long-term immunosuppression. Patients who progress to ESRD may be treated with kidney transplantation after anti-GBM antibodies have been undetectable for several months. Although recurrence of linear IgG staining in the transplant kidney is high (about 50%), these patients are usually asymptomatic and do not require TPE.

It is critical that TPE is implemented early in the course of anti-GBM. Several series have demonstrated that most patients with creatinine less than 6.6 mg/dL recover renal function with treatment. Those with an initial creatinine above 6.6 mg/dL or who are dialysis-dependent at the time of initiation of TPE usually will not recover kidney function due to irreversible glomerular injury. Such patients do not benefit from TPE and it should not be performed unless DAH is present. A lone report of the successful use of immunoabsorption in a patient already on dialysis has not been confirmed. DFPP has also been used rarely. DAH can be rapidly fatal, may have relatively mild manifestations, and responds to TPE in 90% of affected patients. Therefore, a low threshold for initiating TPE is warranted in the presence of DAH.

Rationale for therapeutic apheresis

Because of the presence of autoantibodies and the poor prognosis, TPE was applied to the disorder in the early 1970s. A large number of case reports and case series have since 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. Additional benefits include a more rapid decline in anti-GBM antibody and more rapid resolution of hemoptysis. Despite this, mortality remains high. Reviews suggest that avoidance of ESRD or death will be achieved in 40–45% of patients. The likelihood of a response in the dialysis-dependent patient is very low.

Anti-GBM is predominantly a disease of adults but there have been reports of children as young as 12 months of age being affected by the disorder. These have been in the form of case reports, so limited data are available concerning the behavior of the disorder in this patient population. These patients have been treated similar to adult patients.

Technical notes

In the setting of DAH, plasma should be used for the last portion of the replacement fluid. Of note, some studies have found that patients with DAH but no renal involvement do well irrespective of the use of TPE.

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

In most patients undergoing TPE and immunosuppression, anti-GBM antibodies fall to undetectable levels within 2 weeks so that 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 few patients with the disease and may be present in patients without active disease. In those patients with active disease, TPE should continue until resolution of evidence of ongoing glomerular or pulmonary injury.

References [128–137]

*As of May 1, 2012 using PubMed and the MeSH search terms plasma exchange or plasmapheresis and anti-basement antibody disease for articles published in the English language. References of the identified articles were searched for additional cases and trials.

APLASTIC ANEMIA; ACQUIRED PURE RED CELL APLASIA

Incidence: AA: 2 / 1,000,000; PRCA: rare; PRCA after major ABO mismatched stem cell transplant: 8–26%	**Condition**	**Procedure**	**Recommendation**	**Category**
	Aplastic Anemia	TPE	Grade 2C	III
	PRCA	TPE	Grade 2C	III

# of reported patients*: <100

	RCT	**CT**	**CS**	**CR**
Aplastic Anemia	0	0	2 (6)	5 (5)
PRCA	0	0	2 (7)	19 (26)

AA = aplastic anemia; PRCA = pure red cell aplasia

Description of the disease

Aplastic anemia (AA) and pure red cell aplasia (PRCA) are rare hematopoietic stem cell (HSC) disorders. AA involves pluripotent hematopoietic progenitors and therefore all cell lines are affected, with blood pancytopenia/reticulocytopenia and a hypocellular bone marrow in the absence of neoplastic hematopoiesis, abnormal cellular infiltration or increased reticulin fibrosis. PRCA selectively involves erythroid progenitors and is characterized by normochromic, normocytic anemia, reticulocytopenia (absolute reticulocyte count $<10 \times 10^9$/L), few or no marrow erythroid precursors and normal myelopoiesis, platelet production and lymphocytes. Most cases of AA and PRCA are acquired, however unusual inherited forms exist. Acquired disease can be primary (idiopathic) or secondary, in association with a malignancy (more commonly lymphoid), thymoma (PRCA occurs in 5% of cases), autoimmune or infectious diseases (more commonly viral) or certain drugs and chemicals. Chronic infection with parvovirus B19 in immunocompromised individuals (e.g., AIDS patients) can lead to persistent lysis of erythroid progenitors and PRCA. Acquired PRCA may result from immune-mediated injury of erythroid progenitors by IgG antibodies, cytotoxic T lymphocytes (CTLs) and/or their soluble inhibitory or proapoptotic cytokines. Over 200 cases of acquired PRCA have been reported in patients treated with recombinant human erythropoietin formulations that induced anti-erythropoietin antibodies. PRCA occurs as a post-transplant complication in 8–26% of major ABO mismatched allogeneic stem cell transplants. Donor erythropoiesis is inhibited by persistent host anti-donor isohemagglutinins. The risk of post-transplant PRCA is greater with group A donors into group O recipients and following nonmyeloablative conditioning regimens. Pretransplant TPE, immunoadsorption or other strategies have been used to reduce host isohemagglutinin titers and these maneuvers appear to mitigate the risk of PRCA (see fact sheet on ABO incompatible HSC transplantation). Primary acquired PRCA may present at any age with symptoms of severe hyporegenerative anemia. By comparison, acquired AA occurs most commonly between the ages of 15–25 years with a second smaller peak after age 60 years. The majority of AA cases are idiopathic, with pancytopenia and symptom onset occurring abruptly or insidiously over weeks to months. Patients present with bleeding and bruising (most common) along with anemia and/or infection. AA is classified according to the degree of peripheral blood pancytopenia. Severe AA is defined as bone marrow cellularity <30% and two of three peripheral blood criteria: absolute neutrophil count (ANC) $<0.5 \times 10^9$/L, platelet count $<20 \times 10^9$/L or reticulocyte $<40 \times 10^9$/L and no other hematologic disease.

Current management/treatment

For both AA and PRCA, any possible underlying, reversible triggering etiologies such as drugs, malignancies or infections should be sought and treated. All potential offending drugs (including erythropoietin in PRCA) should be discontinued. IVIG is indicated for chronic active parvovirus B19 infection in immunocompromised patients with PRCA. Surgical resection may be curative for PRCA associated with thymoma. Immunosuppressive therapies are indicated for other etiologies and HSC transplantation is considered for selected patients. The treatment of choice for severe AA in newly diagnosed patients <40 years of age is allogeneic HSC transplantation using bone marrow from an HLA matched sibling donor. Long-term survival rates after matched, related-donor transplantation for AA exceed 70% in adults and over 90% in patients under age 20 years. Similar survival is reported for HLA-matched unrelated donor HSC transplantation in children and younger adults however, morbidity is greater because of higher rates of graft-versus-host disease and therefore nontransplant therapies are often preferred in patients without a sibling donor. Older patients with AA or younger patients with mild disease or lacking a matched donor are treated with immunosuppressive agents, typically horse anti-thymocyte globulin (ATG) and cyclosporine. Hematopoietic growth factors and androgens are also sometimes used as adjunctive therapies. The response rate to immunosuppressive therapy, with recovery to normal or adequate blood counts, ranges from 60–70%. Primary acquired PRCA is also usually responsive to immunosuppressive therapy. Corticosteroids alone (e.g., prednisone at 1 mg/kg/day) yields a 40% response rate. If no response is achieved after 2–3 months of primary treatment for either AA or PRCA, salvage, alternative immunosuppressive agents are available. These include cyclophosphamide, azathioprine, rabbit ATG, rituximab, alemtuzumab and high-dose IVIG. For PRCA, no data favor one salvage regimen over the other. Matched sibling donor HSC transplantation has been used for selected cases of refractory PRCA. Matched HSC transplant should also be considered for older patients with refractory severe AA. For younger patients with refractory AA and no matched donor, cord blood transplantation may be an option. TPE has rarely been used with immunomodulatory treatments for patients with PRCA induced by recombinant human erythropoietin. Post-transplant PRCA in the setting of major ABO mismatch usually recovers with early withdrawal of immunosuppression (cyclosporine) and supportive transfusion care. Persistent cases may respond to exogenous erythropoietin, rituximab, donor lymphocyte infusions and/or TPE.

Rationale for therapeutic apheresis

Because these diseases may be immunologically mediated, TPE may be helpful by removing serum antibody and/or soluble inhibitory factors. Anecdotal reports of benefit using TPE for PRCA and severe AA with concomitant autoimmune diseases suggest that this could be considered as an adjunctive therapy especially those who are unresponsive to conventional immunosuppressive therapies and when there is no option for HSC transplantation. TPE may also improve post-transplant PRCA in the setting of a major ABO-mismatched donor by removing persistent host isoagglutinins (see fact sheet on ABO incompatible HSC transplantation) and in the setting of erythropoietin-induced red cell aplasia by removing anti-erythropoietin antibodies.

Technical notes

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

Duration and discontinuation/number of procedures

Until recovery of hematopoiesis or adequate RBC production. No well-defined treatment schedules exist, however 1–24 treatments were reported in the literature.

References [138–156]

*As of July 3, 2012 using PubMed and the MeSH search terms aplastic anemia, PRCA, plasmapheresis and plasma exchange for articles published in the English language. References of the identified articles were searched for additional cases and trials.

AUTOIMMUNE HEMOLYTIC ANEMIA: WARM AUTOIMMUNE HEMOLYTIC ANEMIA; COLD AGGLUTININ DISEASE

Incidence: 0.8/100,000/yr	**Condition**	**Procedure**	**Recommendation**	**Category**
	Severe WAIHA	TPE	Grade 2C	III
	Severe CAD	TPE	Grade 2C	II

# of reported patients*: <100

	RCT	**CT**	**CS**	**CR**
WAIHA	0	0	1 (3)	20 (21)
CAD	0	0	2 (6)	20 (23)

CAD = cold agglutinin disease; WAIHA = warm autoimmune hemolytic anemia

Description of the disease

Autoimmune hemolytic anemia (AIHA) represents a group of disorders in which autoantibodies mediate either intravascular red cell destruction by the terminal lytic complex (C5b-C9) or, more often, extravascular destruction in the spleen by the macrophage-phagocytic system. The presenting symptoms include fatigue and jaundice. The laboratory findings are of hemolysis (anemia, hyperbilirubinemia, elevated serum LDH), as well as a positive direct antiglobulin (Coomb's) test. AIHA can be classified into two major types, warm autoimmune hemolytic anemia (WAIHA) and cold agglutinin disease (CAD)/cold autoimmune hemolytic anemia (CAIHA). Warm autoantibodies consist of IgG hemolysins that react optimally at 37°C and some may demonstrate relative specificity to red cell 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., methyldopa cephalosporins). In WAIHA, the direct antiglobulin test is positive with anti-IgG and may additionally be positive with anti-C3. CAD results from IgM autoantibodies that react optimally at 0–5°C and may be directed against the red cell I/i antigens. It is typically seen in the post-infectious setting (as polyclonal autoantibodies) or in lymphoproliferative disorders (as monoclonal autoantibodies). The cold-reactive IgM autoantibody produced after *Mycoplasma pneumoniae* infection typically has anti-I specificity, whereas the autoantibody associated with Epstein-Barr virus infection (infectious mononucleosis) demonstrates anti-i specificity. A few cases of tacrolimus associated CAD have recently been described. In CAD, the direct antiglobulin test is positive with anti-C3 only. The severity of hemolysis in AIHA may be influenced by the titer of the autoantibody, its avidity for the relevant RBC antigens, its ability to fix complement, and, for cold autoantibodies, the thermal amplitude. The thermal amplitude is defined as the highest temperature at which the antibody reacts with its cognate antigen. A cold autoantibody with high thermal amplitude can be active within a range of temperatures attainable in vivo. The thermal amplitude of a cold agglutinin may be more predictive of the severity of hemolysis than its titer.

Current management/treatment

Therapy for WAIHA is typically initiated with prednisone (1–2 mg/kg/day) and continued until an adequate response is attained. Prednisone suppresses antibody production and down-regulates Fc-receptor-mediated red cell destruction in the spleen. Splenectomy, despite being underutilized, is perhaps the most effective and best-evaluated second-line therapy, but there are still only limited data on long-term efficacy. Rituximab is another second-line therapy with documented short-term efficacy, but there is limited information on long-term efficacy and side effects. In patients with CAD and severe hemolytic anemia, treatment primarily involves avoiding exposure to cold. In patients who have severe disease, the most effective and best-evaluated treatment is rituximab in the standard lymphoma dose. Prednisone is usually ineffective, as is splenectomy, because the liver is the dominant site of destruction of C3b-sensitized red cells. In a recent prospective study, 20 of 27 patients with CAD responded to rituximab treatment. Recently, newer drugs such as eculizumab and bortezomib have also shown promise in the treatment of CAD. Patients with secondary CAD typically respond well to anti-lymphoma chemotherapy.

Rationale for therapeutic apheresis

TPE may remove pathogenic immune complexes, activated complement components and circulating autoantibodies. TPE is typically utilized in patients with fulminant hemolysis who are unresponsive to RBC transfusion. TPE treatment may temper the disease course until immunosuppressive therapy takes effect, or if other treatments have failed. Several case reports/series have shown favorable results with the use of TPE in WAIHA. However others demonstrate no effect. In one case series utilizing TPE in the setting of severe WAIHA, patients who received TPE prior the RBC transfusions did not demonstrate any enhancement in hemoglobin increment compared to those who did not receive TPE. IgM autoantibodies in CAD are primarily intravascular and bind poorly to RBC at body temperature. In either case, improvement of AIHA after TPE is usually temporary, depending on the characteristics and rate of production of the autoantibody and thus should be combined with concomitant immunosuppressive therapy. 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).

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.

Volume treated: 1–1.5 PV **Frequency:** Daily or every other day
Replacement fluid: Albumin

Duration and discontinuation/number of procedures

Until hemolysis decreases and the need for transfusions is limited or until drug therapy takes effect.

References [157–173]

*As of September 25, 2012 using PubMed and the MeSH search terms warm/cold autoimmune hemolytic anemia, CAD, plasma exchange, plasmapheresis for reports published in the English language. References of the identified articles were searched for additional cases and trials.

BABESIOSIS

Incidence: Rare ($<1/1 \times 10^6$); endemic in Northeast and Great Lakes regions of US	**Condition**	**Procedure**	**Recommendation**	**Category**
	Severe	RBC exchange	Grade 1C	I
	High risk population	RBC exchange	Grade 2C	II

# of reported patients*: <100			
RCT	**CT**	**CS**	**CR**
0	0	3 (14)	14(15)

Description of the disease

Human babesiosis is a tick-borne infectious disease caused by an intraerythrocytic protozoan. The four babesia species that most commonly infect human are: *B. microti,* the predominant US pathogen, *B. duncani, B. divergens* and *B. venatorum*. Endemic areas are the coastal and inland regions of the Northeast, as well as northern Midwest particularly Wisconsin and Minnesota.

The disease is usually transmitted from an animal reservoir to humans by the bites of ixodes ticks, most commonly between May through October. Babesiosis can be also acquired by transfusion of contaminated blood products, typically fresh or frozen RBCs from asymptomatic blood donors. Several cases of neonatal babesiosis acquired by transplacental transmission have been reported. The incubation period is usually 1–3 weeks, with longer incubation period (6–9 weeks) reported with transfusion transmission.

Three types of distinct presentations have been described: 1. Asymptomatic infection which can persist for months-years; this is suggested by the disparity between seroprevalence (0.3–17.8%) and the number of reported cases (44 per 100,000 based on CMS report in Connecticut which is highest in the US). 2. Mild-moderate illness, most common presentation, characterized by the gradual onset of malaise and fatigue followed by intermittent fever and one or more of the following: chills, sweat, anorexia, headaches, myalgia, arthralgia and cough. The illness usually lasts for several weeks to months, occasionally with prolonged recovery that can last more than a year with or without treatment. 3. Severe disease which generally occurs in people with underlying immunosuppressive conditions that include HIV, malignancy, immunosuppressive medication, and after splenectomy. Other risk factors include: age >50 years and simultaneous infection with Lyme disease. Symptoms in severe disease may include acute respiratory failure, disseminated intravascular coagulation (DIC), congestive heart failure, acute liver and renal failure, and hemolytic anemia. Excessive cytokine production is thought to be a major cause of severe babesiosis and is associated with tissue pathology that can lead to significant end-organ damage and can result in persistent relapsing disease or death.

Laboratory testing is required for diagnosis. Specific diagnosis is made through microscopic identification of the organism using Giemsa-stained thin blood smear, DNA amplification using polymerase chain reaction or serologic testing using indirect immunofluorescent assay (IFA). The detection of IgM is indicative of recent infection while IgG titer of 1024 or greater usually signify active or recent infection. Titers generally return to 64 or less within 8–12 months but may persist for years. 1–10% of the RBCs are parasitized in normal hosts, but seldom exceeds 5%. In immunocompromised host, parasitemia up to 85% has been described.

Current management/treatment

Primary therapy for mild to moderate disease includes antibiotic combination. Most people can be successfully treated with atovaquone and azithromycin administered for 7–10 days. Combination of quinine sulfate and clindamycin, the first drug combination used in this disease, is equally effective but associated with more adverse reactions. Thus, this combination should be used when patients do not respond well to atovaquone and azithromycin. In severe disease, the combination of quinine sulfate and clindamycin, given 7–10 days is the treatment of choice. RBC exchange is indicated for babesiosis patients with heavy parasitemia (>10%) or who have significant comorbidities such as significant hemolysis, DIC, pulmonary, renal, or hepatic compromise. In persistent relapsing disease, antibiotics should be given for a minimum of six weeks and for at least two weeks after the last positive blood smear. Due to high morbidity and mortality rate associated with *B. divergens* infections, it is recommended that these infections be treated with RBC exchange and the antibiotic combination of clindamycin and quinine.

Rationale for therapeutic apheresis

The use of RBC exchange transfusion in babesiosis reflects the larger experience with its use in malaria. RBC exchange might influence the course of the disease by three possible mechanisms of action. First, it helps to lower the level of parasitemia by physically removing the infected RBCs from the blood stream and replacing them with noninfected RBCs. Because babesia organisms do not have an exo-erthrocytic phase, removal of RBC-associated parasites might be very effective. Second, by removal of rigid infected cells, RBC exchange could decrease obstruction in the microcirculation and tissue hypoxia caused by adherence of RBCs to vascular endothelium. Finally, the hemolytic process produces vasoactive compounds, including a variety of cytokines (including INF-γ, TNF-α, IL-1, IL-6), nitric oxide and thromboplastin substances, which can promote renal failure and DIC. RBC exchange may help to remove the proinflammatory cytokines. 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 RBC transfusions.

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 RBC exchange can reduce the fraction of remaining patient RBCs to roughly 10–15% of the original. In critically ill patients who failed antimicrobials and/or RBC exchange, the use of TPE has been also reported. For patients with severe coagulopathy, plasma may be incorporated into replacement fluid, either by performing whole blood exchange or TPE.

Volume treated: 1–2 total RBC volume **Frequency:** Single procedure but can be repeated
Replacement fluid: Leukoreduced RBCs

Duration and discontinuation/number of procedures

The specific level of parasitemia to guide when to perform RBC exchange is not clear. Ten percent is the most common used guideline as well as severe symptoms. 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 is based on the level of parasitemia postexchange as well as the clinical condition (ongoing signs and symptoms).

References [174–182]

*As of March 12, 2012 using PubMed and the MeSH search terms Babesiosis and erythrocytapheresis, red cell exchange, exchange transfusion for articles published in the English language. References of the identified articles were searched for additional cases and trials.

BURN SHOCK RESUSCITATION

Incidence: Unknown	**Procedure** TPE	**Recommendation** Grade 2B	**Category** III
# of reported patients*: 100–300			
RCT	**CT**	**CS**	**CR**
1 (17)	2 (66)	6 (102)	0

Description of the disease

Major thermal injury involving greater than 25% total body surface area (TBSA) results in clinically significant, potentially fatal physiologic consequences. Increased capillary permeability and intravascular volume deficits predispose to cellular shock due to diminished organ perfusion. Disruption of the sodium-potassium membrane pump results in an intracellular sodium shift contributing to the progressive hypovolemia. Heat injury causes release of inflammatory mediators with subsequent vasodilation and capillary leakage. Decreased myocardial contractility and inappropriate cardiac output may produce hemodynamic fragility. ARDS may complicate the clinical picture due to inhalational injury or excessive edema with fluid resuscitation. Life threatening infections occur due to suppressed leukocyte chemotactic function, lymphocyte suppression, and loss of the normal skin barrier. Circulating mediators have been implicated in these physiologic derangements, although the exact mechanisms or humoral "factor(s)" remain enigmatic. Decreased fibronectin in severely burned patients have been correlated with impaired function of the reticuloendothelial system and phagocytosis. Microembolization of tissue debris, bacteria, and byproducts of DIC are other potential contributors to the pathophysiology of burn shock.

Current management/treatment

The treatment in the immediate postburn period is aggressive intravenous fluid resuscitation with crystalloid. Practice guidelines published by the American Burn Association indicate that the volume of fluid resuscitation is based on estimated of body size, surface area and extent of burns, typically 2–4 mL/kg body weight / %TBSA of crystalloid in the first 24 h. Goals are to maintain urine output (UOP) while balancing risks of edema, ARDS and organ hypoperfusion. Fluid resuscitation is successful in most burn patients. Patients with full-thickness burns, inhalation injury or delay in resuscitation may have greater fluid requirements. The most common solution is Lactated Ringers (LR); other solutions such as hypertonic saline or colloids, such as 5% albumin or hydroxyethyl starch, are also incorporated into different fluid resuscitation strategies.

Rationale for therapeutic apheresis

The theoretical benefit to TPE in the setting of acute burn shock is based on the removal circulating factors such as inflammatory mediators or other humoral substances participating in major burn pathophysiology. Replacement with donor plasma hypothetically could facilitate decrease in capillary permeability, and improve intravascular oncotic pressure, which might improve response to fluid resuscitation, increase mean arterial pressure (MAP), increase UOP, and possibly improve immune function by providing consumed factors and removing mediators. TPE has also been reported to decrease lactate levels. Specific mediators in the circulation have not been characterized but cross perfusion studies from burned to unburned dogs caused a decrease cardiac output in the unburned animals and in-vitro studies of human burn patients demonstrate that specific immune cellular abnormalities can be reversed when the cells are removed from the burn environment, such as placement in plasma from a healthy individual.

TPE did not alter the course of burn shock in the single published randomized control trial of 17 patients (9 TPE arm; 8 control arm) (*Kravitz*). However, mean full-thickness burn injury was significantly higher in the TPE group. Completion of resuscitation was accomplished earlier in the TPE group. There were three deaths in the TPE group versus none in the control group. A retrospective historic controlled trial of 40 patients (*Neff*) found that TPE increased MAP and UOP in the treated group and decreased the estimated intravascular fluid volumes required for resuscitation by 30%. Survival was equivalent between the groups but as the TPE treated group had more severe burns, higher mortality would have been predicted. These survival results are confounded, however, by the fact that the mortality in both groups was greater than predicted. Finally, a trial looking at immunologic parameters in 26 burn patients compared the 13 who had undergone TPE to those who had not with regard to a variety of immunologic markers (*Stratta*). No differences were seen except that serum from patients undergoing TPE had less suppression of the mixed lymphocyte reaction. The TPE group had greater extent of burn injury and longer hospitalization but equivalent mortality to those less ill patients who had not received TPE. Of the limited published case series, a variety of favorable physiologic effects were reported with respect to fluid resuscitation, UOP, cardiac function and immune benefits. Clinical outcome data were not consistently available. In one case series (*Stratta*), TPE was applied in five clinical settings (number of surviving patients/total number of patients treated): failed fluid resuscitation (9/10), myoglobinuria (2/3), respiratory failure ARDS (3/4), metabolic "exhaustion" (4/6), and documented sepsis (1/5); however, the endpoint for clinical follow-up was not defined in this study. Overall mortality with TPE was 33% without a control group for comparison. A recent case series of 37 patients (*Klein*) found statistically significant increased UOP and decreased crystalloid volume needed when comparing these parameters 3 h before and 3 h after TPE.

Further investigation with well-designed randomized controlled trials is needed to establish the efficacy and safety of TPE in this setting. The American Burn Association acknowledges that TPE is sometimes applied empirically as a salvage therapy; however, it does not recommend TPE outside the context of a clinical trial.

Technical notes

TPE was instituted early in the postburn period, typically 8–16 h after injury. Patients treated with TPE had greater than 20–50% TBSA burns and were refractory to fluid resuscitation in most reports. In the retrospective historic controlled trial, TPE was initiated if the total resuscitation volumes exceeded 1.2X the volume predicted by the modified Baxter formula (3 cm^3LR/kg/%TBSA) to be necessary to keep UOP >50 cm^3/h. and/or MAP $\geq$65 mmHg. TPE adverse reactions were infrequently reported in these studies although it is not clear if this was related to absence of adverse reaction reporting in the case study design or true tolerance of the TPE procedure.

Volume treated: 1.5 TPV	**Frequency:** Once, see below
Replacement fluid: Plasma, albumin	

Duration and discontinuation/number of procedures

Most reports performed a TPE within the first 24 h (8–16 h) postburn with additional 1 or 2 TPE procedures in select patients. In the retrospective historic controlled trial, patients whose MAP and UOP did not increase or whose IV fluid volumes did not decline to predicted volumes received a second TPE within 6–8 h of the first.

References [183–196]

*As of October 21, 2012 using PubMed and the MeSH search terms burn and shock and plasma exchange or plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

CARDIAC TRANSPLANTATION (HUMORAL/CELLULAR REJECTION; ABO-COMPATIBLE)

Incidence: ~2300 transplants performed per year in the US; Rejection prophylaxis: Infrequent; Cellular rejection: 21–30% in 1st post-transplant yr; Desensitization/AMR rates: Unknown	**Condition**	**Procedure**	**Recommendation**	**Category**
	Rejection prophylaxis	ECP	Grade 2A	II
	Cellular/ recurrent rejection	ECP	Grade 1B	II
	Desensitization	TPE	Grade 2C	III
	AMR	TPE	Grade 2C	III

# of reported patients*: ECP: 100–300; TPE: 100–300

	RCT	**CT**	**CS**	**CR**
Rejection prophylaxis	1 (60)	2 (38)	0	0
Cellular rejection	0	0	4 (58)	2 (4)
Desensitization	0	4 (76)	5 (26)	2 (2)
AMR	0	0	>10 (>171)	4 (8)

AMR = antibody mediated rejection

Description of the disease

Major advances in immunosuppression have significantly enhanced survival and quality of life for cardiac transplant patients, although infection, malignancies and allograft rejection continue to threaten long-term survival. Cardiac allograft rejection may be hyperacute (in cases of ABO or major HLA incompatibility), acute antibody-mediated (AMR), acute cellular (ACR), or chronic rejection (allograft vasculopathy). ACR is the most common type of rejection and is mediated by T cells. The diagnosis of ACR is made by histologic examination of endomyocardial biopsies of the right ventricle, which show inflammation and myocyte damage. AMR is mediated by antibodies directed to the allograft and is more likely to cause hemodynamic instability with or without histologic evidence of immunoglobulin and/or complement deposition in tissue. AMR is also suspected in the setting of interstitial edema, prominent endothelial cells lining the cardiac microvasculature and intravascular histiocytes. Often, the only sign of AMR is decreased ventricular ejection fraction. The prognosis of AMR is worse than ACR; AMR is a strong risk factor for the early development of allograft vasculopathy. Young age, female gender, history of congenital heart disease, high titer of HLA antibodies, positive pretransplant crossmatching, sensitization to OKT3, or prior exposure to cytomegalovirus increase the risk of AMR. AMR and ACR may be seen alone or in combination. Chronic rejection or allograft vasculopathy occurs months to years post-transplant and its mechanism is poorly understood. It is characterized by progressive intimal thickening of the coronary arteries leading to late graft failure. In addition to drug-specific side effects, cardiac allograft recipients have a high risk of developing infections, the major cause of death in the first post-transplant year. There is also an increased lifetime risk of immunosuppression-induced malignancies, reaching 35% at 10 years post-transplant. Malignancy is the second most common cause of death, behind allograft vasculopathy, in patients who survive 5 years following transplant. This fact sheet does not discuss neonatal ABO-incompatible cardiac transplantation, where whole blood exchange from the cardiopulmonary bypass circuit is employed to decrease levels of donor-specific ABO isohemagglutinins.

Current management/treatment

ECP has been advocated as a therapy to improve outcome after recalcitrant/severe rejection. In the largest study on this topic, ECP treatment decreased rejection risk significantly, despite patients selected for ECP being at the greatest risk for rejection (*Kirklin*). The hazard for subsequent rejection or death secondary to rejection was significantly reduced toward the risk-adjusted level of lower-risk non-ECP treated patients. In a randomized controlled trial examining the role of ECP in the prevention of rejection in cardiac transplantation (*Barr*), after 6 months of post-transplant follow-up, the number of episodes of acute rejection per patient was significantly lower in the ECP arm. However, there was no significant difference in the time to the first episode of rejection, the incidence of rejection associated with hemodynamic compromise, or survival at 6 and 12 months. Of note, the standard immunosuppression used in the study included cyclosporine, azathioprine, and prednisone, and not tacrolimus/MMF-based protocols typically used in more recent transplants (long-term follow up of outcomes from this study has not been published). In another controlled study from the same group, patients in the ECP group had a significant reduction in PRA levels at two time points within the first 6 postoperative months. In comparison to the control group, coronary artery intimal thickness was also significantly reduced in the ECP group at 1-yr follow-up.

Highly sensitized patients in need of cardiac transplantation face major challenges in obtaining a compatible allograft. Several transplant programs around the US and the world have embarked on desensitizing such patients to enable them to receive allografts from a larger number of potential donors. A recent report from a consensus conference on the sensitized patient awaiting heart transplantation discusses several aspects of this process (*Kobashigawa*). Several programs treated patients with pretransplant PRAs >50% and typically use a combination of TPE, IVIG, and rituximab. Outcomes (rejection/survival) rates compared to nonsensitized transplants have been examined in multiple studies, with some studies showing equivalence, while others have demonstrated poorer outcomes in sensitized patients. Finally, TPE has been used in conjunction with enhanced immunosuppression in the setting of AMR of the cardiac allograft. All studies have been observational and retrospective in nature. Newer trends in identification of pathogenic donor specific HLA antibodies include use of a novel C1q assay to detect a subset of IgG antibodies capable of fixing complement.

Rationale for therapeutic apheresis

Apheresis techniques have both complemented, and helped avoid the intensive use of immunosuppressive drugs to prevent and/or manage cardiac allograft rejection. Although the mechanism of ECP is not exactly known, recent data suggest that it decreases levels of effector T cells while at the same time expanding regulatory T cells (Tregs). The number of circulating Tregs in transplant patients treated with ECP has been shown to increase following ECP. The goal of TPE is to remove donor-specific antibodies and/or inflammatory mediators implicated in AMR. Thus, while ECP is used on a chronic basis as an immunomodulatory agent, TPE's role is in the acute setting of rejection/desensitization. Newer monoclonal antibodies such as bortezomib are increasingly being used in addition to TPE for the desensitization of highly sensitized patients, and in the treatment of rejection.

Technical notes

In low body weight patients, ECP may require protocol adjustments to compensate for the extracorporeal volume during the procedure. While it is unknown whether a certain minimum dose of mononuclear cells (MNCs) need to be treated to mediate the benefits of ECP, it is advisable to draw a CBC prior to the procedure to ensure that there are circulating MNCs. Lymphopenia is not uncommon in this patient population.

Volume treated: ECP: MNC product typically obtained after processing 1.5 L of blood. The two step process method collects and treats MNCs obtained from 2 TBV processing; TPE: 1–1.5 TPV
Replacement fluid: ECP: NA; TPE: Albumin, plasma

Frequency: ECP: Two procedures on consecutive days (one series) weekly or every 2–8 weeks for several months (regimens vary widely); TPE: Daily or every other day

Duration and discontinuation/number of procedures

There are no clear criteria for discontinuing treatment in ECP. Treatments are typically continued until improvement/ stabilization of symptoms occur. For TPE, improvement in cardiac function, biopsy findings, and donor specific antibody levels are often used to determine timing of discontinuation of treatments.

References [197–225]

*As of September 30, 2012 using PubMed and the MeSH search terms heart/cardiac transplantation, cellular rejection, humoral rejection, transplant vasculopathy, photopheresis, plasmapheresis, plasma exchange, desensitization for articles published in the English language. References of the identified articles were searched for additional cases and trials.

CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

Incidence: Very rare (282 cases in CAPS Registry)	**Procedure** TPE	**Recommendation** Grade 2C	**Category** II

# of reported patients*: 100–300[+]

RCT	CT	CS	CR
0	0	6 (60)	29 (33)

[+]According to the CAPS Registry, 109 patients have received TPE.

Description of the disease

The antiphospholipid syndrome (APS) is an acquired hypercoagulable state characterized by one or more episodes of venous and/or arterial thrombosis and/or obstetric complications in a patient with laboratory evidence of antiphospholipid antibodies such as lupus anticoagulant, anticardiolipin and/or anti-β_2-glycoprotein I. Catastrophic APS (CAPS) was first described in 1992 by Asherson, as an uncommon variant of APS that results in multiorgan failure. CAPS is defined as the acute onset of multiple thromboses in at least three organ systems over a period of days or weeks, in patients with antiphospholipid antibodies. The most commonly affected sites by thrombosis are small vessels of the kidneys, lungs, brain, heart and skin, although large vessel thrombosis may also occur. Common manifestations of CAPS include acute kidney injury, 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. CAPS may be the first manifestation of APS ("de novo") or complicate the course of patients known to have the syndrome. It is unknown why a minority of patients with APS present with a catastrophic picture. In the CAPS Registry, 53% of 282 patients are presumed to have precipitating factors which preceded the clinical diagnosis of CAPS: infection was the most common finding, affecting 22% of the patients, followed by surgical procedures at 10%, warfarin withdrawal or low international normalized ratio (INR) (8%), medications (7%), obstetric complications (7%), neoplasia (5%) and systemic lupus erythematosus (SLE) flare (3%). Relapses occurred in 8 registry patients and mortality approached 50% and is mainly due to myocardial thrombosis with or without respiratory failure. Thrombocytopenia can be marked and 20% of CAPS patients present with DIC. Over 33% of patients have hemolysis which is secondary to DIC or Coombs positive immune hemolysis. However, schistocytes are only rarely seen, and help differentiate CAPS from other thrombotic microangiopathies such as thrombotic thrombocytopenic purpura (TTP) and HUS. More than 80% of patients with CAPS have serological evidence of lupus anticoagulant and IgG anticardiolipin antibodies. IgM is seen in less than 40% of cases.

Current management/treatment

The optimal treatment of CAPS is still debatable since there have been no prospective studies due to the rare status of the condition. However, the therapeutic approach has three clear aims: treat any precipitating factors (i.e., infection, necrotic organ, etc.), prevent and control ongoing thrombosis, and suppress the excessive cytokine production. Cervera et al. published several reviews of outcomes of 280 patients entered into the CAPS Registry. They found that 44% did not survive the acute episode and that recovery was significantly associated with the use of anticoagulants (63% vs. 22%, $P < 0.0001$; odds ratio [OR] 6, 95% confidence interval [CI] 2.8–13.8). The authors also noted that most patients received multiple treatments, and that the combination with the best outcome was anticoagulants, corticosteroids, and TPE and/or IVIG. Although some patients also received cyclophosphamide to halt antibody production, the data are not conclusive about its role in CAPS unless the patient has a flare of SLE. A 2012 report by Shapira and others includes a single case of severe recurrent CAPS despite aggressive therapy as above that eventually responded to eculizumab.

Rationale for therapeutic apheresis

The exact mechanism of TPE benefit in CAPS is not known, although the removal of antiphospholipid antibodies, cytokines, tumor necrosis factor-α, and complement likely play an important role. Furthermore, since plasma has been used as the replacement fluid in the majority of reported cases, repletion of natural anticoagulants such as antithrombin and proteins C and S is also likely contribute to the overall benefit of the procedure. Two successful reports using albumin as replacement fluid claim that plasma may not be always necessary in CAPS. Since plasma antithrombin is essential to mediate anticoagulation with heparin, the use of albumin alone as replacement fluid may prevent the beneficial effect of heparin unless levels of antithrombin are serially monitored and heparin anticoagulation is adequate by laboratory monitoring. Thus, it is likely that a combination of plasma and albumin would provide the necessary benefit of TPE and minimize potentially serious and undesirable side-effects from excessive exposure to plasma.

Technical notes

Plasma was used in most reported cases; efficacy of albumin has not been widely tested.

Volume treated: 1–1.5 TPV **Frequency:** Daily
Replacement fluid: Plasma (albumin alone is rarely used)

Duration and discontinuation/number of procedures

Most published cases have reported daily TPE for a minimum of 3–5 days. Clinical response dictates the duration of TPE; no single clinical or laboratory parameter is used to determine when to discontinue treatment. Some patients have been treated for weeks instead of days.

References [226–244]

*As of September 6, 2012 using PubMed and journals published in English language using the search terms catastrophic antiphospholipid syndrome (CAPS), antiphospholipid syndrome, lupus anticoagulant, anticardiolipin antibodies, plasma exchange, plasmapheresis. References of the identified articles were searched for additional cases and trials.

CHRONIC FOCAL ENCEPHALITIS (RASMUSSEN ENCEPHALITIS)

Incidence: Rare	**Procedure**	**Recommendation**	**Category**
	TPE	Grade 2C	III
	IA	Grade 2C	III

# of reported patients*: <100

	RCT	**CT**	**CS**	**CR**
TPE	0	0	2 (9)	3 (5)
IA	0	0	1 (3)	1 (1)

Description of the disease

This syndrome of chronic encephalitis was originally described in three children by Theodore Rasmussen in 1958. The hallmarks of the syndrome are intractable focal seizures (epilepsia partialis continua) resistant to anticonvulsant drugs, and progressive unilateral cerebral atrophy leading to progressive hemiparesis, loss of function in the affected cerebral hemisphere and cognitive decline. Patients may exhibit recurrent status epilepticus. Onset is typically in childhood (mean age 6.8 ± 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 encephalitis. Cerebrospinal fluid analysis is typically normal, although mild lymphocytic pleocytosis and elevated protein may be found.

Current management/treatment

Anticonvulsants are necessary, but not always effective, nor do they arrest progression of the disease. Subtotal, functionally complete hemispherectomy may markedly reduce seizure activity in a majority of patients but results in permanent contralateral hemiplegia. Intravenous methylprednisolone and oral prednisone given for up to 24 months in a tapering schedule may help to diminish epilepsia partialis continua and motor deficits during the first year of onset and before hemiplegia develops. IVIG up to 2 g/kg over 2–5 days, then repeated monthly if there is a response, may be tried prior to a trial of steroids in patients with established disease and may modestly improve the hemiparesis. Some authors recommend intravenous methylprednisolone (400 mg/m^2 every other day for three infusions followed by monthly infusions for the first year) and prednisone (2 mg/kg/day tapered over 1 to 2 years) if further treatment is needed. Intraventricular interferon-α given via Omaya reservoir, intravenous rituximab and tacrolimus have been investigated for control of epileptic and neurological aspects of Rasmussen's syndrome. Ganciclovir has been also used and showed some therapeutic effect in patients treated early after appearance of symptoms (1–3 months).

Rationale for therapeutic apheresis

Patients may have autoantibodies, against several neural molecules, that may be produced in the CNS after cytotoxic T cell-mediated neuronal damage. The demonstration of serum immunoreactivity to the glutamate receptor GluR3 in three individuals with histologically confirmed Rasmussen's syndrome led to the use of TPE in a 9-year-old girl. An initial seven 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. More recent reports indicate that serum GluR3 immunoreactivity is a feature of epilepsy syndromes and not specific to Rasmussen encephalitis, but other brain autoantibodies have been identified in Rasmussen's encephalitis patients. Clinical and EEG parameters of epileptogenesis were transiently diminished by TPE in two other patients. Monthly courses of plasma immunoadsorption using staphylococcal protein A diminished seizure frequency and halted cognitive deterioration in a 16-year-old girl with IgG anti-GluR3 antibodies over a 2-year period, and controlled status epilepticus in a 20-year-old woman. Despite the paucity of clinical reports, a concerted trial of immunotherapy, including apheresis, to control seizures, mitigate functional decline, and delay the need for hemispherectomy in patients with Rasmussen encephalitis could be considered.

Technical notes

Neuropsychological assessment may be helpful in evaluating patients with slowly progressive disease to determine whether TPE is effective in postponing surgical therapy. 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. A similar approach may be taken in subsequent courses if a salutary clinical effect is apparent. Note: Since December 2006, devices used to perform protein A immunoadsorption apheresis have not been commercially available in the US.

Volume treated: TPE: 1–1.5 TPV; IA: 1.5–2 TPV	**Frequency:** TPE: 3–6 TPE over 6–12 days, repeat
Replacement fluid: TPE: Albumin; IA: NA	monthly; Alternative schedule: TPE weekly; IA: 1–3, repeat monthly

Duration and discontinuation/number of procedures

After an initial course of treatment subsequent courses of TPE (with or without IVIG) may be performed at intervals of 1–2 weeks or up to 2–3 months as empirically needed to maintain clinical stability and avoid or delay hemispherectomy. Immunosuppressive medications may increase the interval between courses. Surgical treatment is offered for the management of patients who exhibit functional or cognitive decline or intractable seizure activity despite intensive immunomodulatory therapy.

References [47, 245–256]

*As of October 14, 2012 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.

CHRONIC INFLAMMATORY DEMYLINATING POLYRADICULONEUROPATHY

Incidence: 1–2/100,000	**Procedure** TPE	**Recommendation** Grade 1B	**Category** I
# of reported patients*: >300			
RCT	**CT**	**CS**	**CR**
3 (67)	0	31(1009)	31(32)

Description of the disease

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is characterized by proximal and distal symmetrical muscle weakness, with or without numbness, that progresses and relapses for over two or more months. Neurologic impairment includes decreased sensation and diminished or absent reflexes. Cerebrospinal fluid protein is elevated and evidence of demyelination is present on electrophysiological testing. 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 paraproteinemic polyneuropathies). CIDP is distinct from Guillain-Barré syndrome (AIDP) in that it is a chronic rather than an acute disorder (see fact sheet on AIDP). Similar clinical presentations may be seen with inherited, paraneoplastic and toxic neuropathies, and neuropathies associated with nutritional deficiency, porphyria, or critical illness.

Current management/treatment

Corticosteroids, TPE, and IVIG yield similar treatment outcomes in controlled trials; therefore a choice among them is based on cost, availability, and side effects. Therapies should be initiated early to stop the inflammatory demyelination and prevent secondary axonal degeneration, and therefore permanent disability. Individuals may differ in response to any one of these modalities. Therapeutic response is measured by improvement or stabilization in neurological symptoms, at which point treatment can be tapered or discontinued. Sixty to 80% respond to initial therapy but long-term prognosis varies. Maintenance therapy, including continuing steroids, periodic TPE, or repeated infusion of IVIG, is usually required because discontinuation of therapy may be followed by relapse. Maintenance therapy is dictated by the patient's symptoms and clinical exam. Secondary therapies include rituximab, cyclosporine, interferon, azathioprine, cyclophosphamide, and other immunosuppressive therapies which can be used in conjunction with immunomodulating treatments. Long term studies of CIDP patients treated with IVIG, steroids, and/or TPE demonstrated 39% required continued immunomodulating treatment (29% steroids, 5% IVIG, 5% TPE) and 26% had complete remission, 61% had partial remission (were able to walk), and 13% had severe disability (unable to walk) (*Kuwabara*).

Rationale for therapeutic apheresis

The presumed etiology of CIDP is autoimmune attack on the peripheral nerves. Both humoral and cell-mediated immune responses have been documented. Therapies are aimed at modulation of the abnormal immune response.

In the first double-blind, sham-controlled trial, patients who received TPE (average 47 mL/kg of plasma exchanged) versus sham PE twice weekly for 3 weeks demonstrated significant improvement (*Dyck*). In a randomized double-blind crossover trial, patients received 10 TPE (40–50 mL/kg plasma exchanged) or sham PE procedures over 4 weeks then a 5-week washout period and then received ten of the alternate procedure for 4 weeks (*Hahn*): 80% had substantial improvement in their neurological function, of these 66% relapsed within 1–2 weeks, but responded to continued TPE. In a randomized crossover trial of TPE (twice a week for 3 weeks then once a week for 3 weeks) versus IVIG (0.4 g/kg once a week for 3 weeks then 0.2 g/kg once a week for 3 weeks), both TPE and IVIG resulted in significant improvement but there was no significant difference between the two treatments (*Dyck*).

Technical notes

Volume treated: 1–1.5 TPV	**Frequency:** 2–3 /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 and/or other immunomodulating therapies, 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 [257–266]

*As of April 20, 2012 using PubMed and the MeSH search terms chronic inflammatory demyelinating polyneuropathy and plasma exchange and plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

COAGULATION FACTOR INHIBITORS

Incidence: Hemophilia A patients: 20–30%; Hemophilia B patients: 3–5%; spontaneous FVIII inhibitor: 0.2–1/1,000,000	**Condition**	**Procedure**	**Recommendation**	**Category**
	Alloantibody	TPE	Grade 2C	IV
	Alloantibody	IA	Grade 2B	III
	Autoantibody	TPE	Grade 2C	III
	Autoantibody	IA	Grade 1C	III

# of reported patients*: 100–300

	RCT	**CT**	**CS**	**CR**
TPE	0	0	7 (83)	36(39)
IA	0	0	9(115)	45(64)

Description of the disease

Coagulation factor inhibitors are antibodies that target a specific coagulation factor and can lead to hemorrhage by disrupting the ability to form a stable clot. Patients with moderate to severe congenital FVIII or FIX deficiency (hemophilia A and B, respectively) may make alloantibodies to the replaced factor following exogenous factor replacement (either recombinant or plasma derived). This is one of the most serious complications in the treatment of patients with hemophilia because it can prevent effective factor replacement. It occurs in up to 20-30% of hemophilia A and 3-5% of hemophilia B patients.

Patients without congenital factor deficiency can also make inhibitory antibodies that are either autoantibodies, xenotropic alloantibodies following a foreign factor exposure, or associated with a plasma cell dyscrasia or myeloproliferative neoplasm (MPN). Autoantibodies are usually against FVIII. This rare diagnosis has a biphasic age distribution (elderly and in the post-partum period) and is associated with autoimmune disorders, infections, and malignancy. Cross reactive xenotrophic alloantibodies against FV and prothrombin (FII) have occurred in patients exposed to early formulations of bovine-derived fibrin glue. Development of FV antibodies are also linked to therapy with streptomycin, cefotaxime, tacrolimus, and infections (tuberculosis and HIV). Patients with lupus anticoagulants (LA) may occasionally have selective FII autoantibodies and may present with bleeding and concomitant APS. Acquired von Willebrand syndrome (AVWS) may result from IgG or IgM antibodies that bind VWF and cause increased clearance or abnormal platelet adherence. Monoclonal proteins may also bind to coagulation factors leading to acquired deficiency or functional defects. Acquired FX deficiency is associated with systemic light chain amyloidosis due to selective binding of FX to amyloid fibrils. In this disorder, laboratory measurements of coagulation function and FX activity levels are poor predictors of bleeding risk.

The bleeding tendency with coagulation factor inhibitors is due to clearance of the specific factor by the reticuloendothelial system and/or direct inhibition of the factor function. Specific inhibitory antibodies are quantified and expressed as Bethesda units (BU), an analysis that employs mixing the suspect plasma with normal plasma; <5 BU is considered low titer. When the underlying cause is MPN or plasma cell dyscrasia, the laboratory assays of coagulation function may not accurately reflect the hemostatic derangement and bleeding risk.

Current management/treatment

Therapy for patients with coagulation inhibitors should be individualized, depending on diagnosis, the presence of bleeding and the inhibitor titer. The current treatment options for bleeding in patients with immune-mediated inhibitors include high doses of FVIII for low titer inhibitor (<5 BU) and FVIII bypassing factors for high titer inhibitors (>5 BU). Bypass factors include activated prothrombin complex concentrates and recombinant FVIIa. The treatment options for suppression of inhibitor production include high dose corticosteroids, rituximab, cyclophosphamide, cyclosporine or high dose IVIG, often used in combination. The largest long term series of treatment for acquired inhibitors by Zeitler et al. found 83% 1 year remission rate using a combination approach of 5 days of IA, IVIG, immunosuppression and FVIII. In hemophilia A, immunologic tolerance can be induced by daily infusions of FVIII. Patients with acquired FV inhibitors are usually treated with immunosuppressive therapy, IVIG and platelet and/or plasma transfusion. Patients with AVWS and hemorrhage are usually managed with desmopressin (DDAVP), antifibrinolytic agents, factor replacement therapy, FEIBA, IVIG or recombinant FVIIa. Hypoprothrombinemia (FII) associated with lupus anticoagulants can be treated with prothrombin complex concentrate and corticosteroids. Myeloproliferative neoplasms and plasma cell dyscrasias are treated as above to control bleeding, as well as with definitive therapy of the underlying disorder.

Rationale for therapeutic apheresis

The extracorporeal removal of antibodies with IA is more effective than TPE. Two IA techniques, neither of which are approved in the US, involve either a sepharose-bound staphylococcal protein A (SPA) column (Immunosorba) or a column of sepharose-bound polyclonal sheep antibody against human Ig (Ig-Therasorb). Polyclonal sheep antibodies bind all classes of immunoglobulin causing a large decrease in IgG levels. SPA binding of the specific IgG subclasses 1, 2, and 4 leads to more effective removal of coagulation factor antibodies, which are predominantly IgG_4. SPA has other immune effects, such as complement activation and modulation of in vivo biological responses that are thought to account, at least in part, for its mechanism of action. Case series and reports indicate that IA can effectively decrease antibody titers, improve the response of hemophiliacs to factor replacement, and decrease serious bleeding in patients with spontaneous inhibitors, but clinical response is not observed in all patients. Because IA requires special equipment that is not widely available and expensive, it is often reserved for patients with recalcitrant inhibitors who do not respond to other therapies.

There are no data to support TPE in the clinical setting of specific coagulation factor inhibitors in hemophiliacs or autoimmune disorders. However, TPE can be considered for patients with plasma cell dycrasias or MPNs who are bleeding and refractory to standard interventions, especially those with IgM MGUS because of the efficient removal of IgM. One report described a case of FV deficiency due to cross-reacting xenotropic antibodies being treated with TPE, but the beneficial effect was unclear. TPE has not been found to be useful in light chain amyloidosis with bleeding complications.

Technical notes

To remove inhibitors, plasma flow rates are 35–40 mL/min in Immunosorba; a three plasma-volume treatment (10 L) requires 20–30 adsorption cycles. Anticoagulant should be used at the lowest amount possible. These columns are not available in the US.

Volume treated: TPE: 1–1.5 TPV; IA: 3 TPV **Frequency:** TPE: daily; IA: daily
Replacement fluid: TPE: plasma; IA: NA

Duration and discontinuation/number of procedures

For inhibitors, daily until bleeding can be controlled with other therapeutic modalities.

References [95, 171, 264–282]

*As of October 19, 2012 insert dates 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.

CRYOGLOBULINEMIA

Incidence: About 50% of patients with chronic hepatitis C	**Condition**	**Procedure**	**Recommendation**	**Category**
	Severe/symptomatic	TPE	Grade 2A	I
	Severe/symptomatic	IA	Grade 2B	II

# of reported patients*:100–300

	RCT	**CT**	**CS**	**CR**
TPE	1(57)	0	20(270)	>50
IA	1(17)	0	1(4)	0

Description of the disease

Cryoglobulins are immunoglobulins that reversibly precipitate below body temperature. The aggregates of cryoglobulins can deposit on small vessels and cause damage by activating complement and recruiting leukocytes. This most commonly occurs on the skin of lower extremities because of exposure to lower temperatures. The end-organ complications 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). These disorders result in B cell proliferation possibly due to increase in BAFF (B cell-activating factor) or IgG-bound HCV driving clonal expansion. Mild symptoms include purpura, arthralgia, and sensory neuropathy. Severe symptoms include glomerulonephritis, neuropathy, and systemic vasculits. Cryoglobulins are classified into three types: type I consist of monoclonal immunoglobulins, usually due to multiple myeloma (IgG) or Waldenström's macroglobulinemia (IgM), 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 and characterization of cryoglobulins (including quantitation by the cryocrit).

Current management/treatment

Management is based on the severity of symptoms and treating the underlying disorder. 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 corticosteroids, cyclophosphamide, and rituximab. A recent randomized control trial comparing rituximab (fixed dosing at 1 g/day on days 0 and 14; with corticosteroids) with conventional treatment (corticosteroids plus azathioprine, cyclophosphamide, or TPE) in patients with cryoglobinemic vasculitis with skin ulcers, glomerulonephritis or peripheral neuropathy (93% with HCV infection) demonstrated superior improvement in the rituximab arm. A large case series (CryoVas survey) demonstrated greatest therapeutic efficacy of rituximab plus corticosteroids over corticosteroids alone or with alkylating agents in patients with noninfectious mixed cryoglobulinemia vasculitis. Additionally, interferon and ribavirin are used for the treatment of cryoglobulinemia related to hepatitis C infection. When cryoglobulinemia is associated with severe clinical manifestations such as skin ulcerations, glomerulonephritis or neuropathy, TPE can be used as an adjunct to control the symptoms by directly removing the cryoglobulins.

Rationale for therapeutic apheresis

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, arthralgia and/ or ulcerating purpura. TPE can be performed in conjunction with corticosteroids or cytotoxic agents or alone. It has been used in both the short and long term management. Case series and case reports suggest 70–80% improvement with TPE. Double or 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. Another apheresis modality used in this disease is cryofiltration or cryoglobulinapheresis, which cools the plasma in an extracorporeal circuit either continuously or in a 2 step procedure to remove cryoglobulins, the remaining plasma is warmed to body temperature prior to returning to the patient. Cryofiltration is less efficient at removing cryoglobulins than DFPP. One randomized controlled trial was performed on patients with cryoglobulinemia associated with hepatitis C who had not responded to previous conventional medications. The patients first received 12 weeks of medical therapy and then received another 12 weeks of medical therapy (immunosuppression and anti-virals) with or without immunoadsorption apheresis (IA with dextran sulfate [Selsorb], 3 times a week, 45 mL/kg processed for 12 weeks or less if symptoms resolved). Statistically greater clinical improvement was demonstrated with the use of IA (80% vs. 33%) when response was assessed by using a previous published scoring system that assigns points for each organ's involvement and reflects the severity of involvement. Another randomized controlled trial on patients with severe mixed cryoglobulinemia or cryoglobulinemic vasculitis, mostly due to HCV infection, received standard therapy (TPE, glucocorticoids or azathioprine/cyclophosphamide) or rituximab. The primary outcome was survival of treatment, which was 71.4% for rituximab group and 3.5% for nonrituximab group at 6 months. Additionally, the patients receiving rituximab had improvement in disease activity (Birmingham Vasculitis Activity Score). Thus, rituximab may be a superior first line therapy for severe disease.

Technical notes

It is prudent to warm the room, draw/return lines, and/or replacement fluid. There is a single case report of a patient receiving plasma exchange who developed acute oliguric renal failure due to infusion of cold plasma and precipitation of cryoglobulin within glomerular capillary loops. Other cases have reported cryoglobulin precipitation in the extracorporeal circuit.

Volume treated: 1–1.5 TPV **Frequency:** Every 1–3 days
Replacement fluid: Albumin, plasma

Duration and discontinuation/number of procedures

The reports use a variety of number of treatments and frequencies. For acute symptoms, performance of 3–8 procedures, and re-evaluation for clinical benefit should be considered. TPE may rapidly improve acute symptoms and serve as a bridging therapy prior to treating the underlying disease and reducing immunoglobulin production with immunosuppressive drugs. Weekly to monthly maintenance treatments may be indicated in patients who initially responded to TPE in order 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 [118, 283–290]

*As of September 17, 2012 using PubMed and the MeSH search terms cryoglobinemia and plasmapheresis, plasma exchange, and immunoadsorption for articles published in the English language. References of the identified articles were searched for additional cases and trials.

CUTANEOUS T CELL LYMPHOMA; MYCOSIS FUMNGOIDES; SEZARY SYNDROME

Incidence: MF: 6/1,000,000/yr; SS: 0.8/1,000,000/yr	**Condition**	**Procedure**	**Recommendation**	**Category**
	Erythrodermic MF + SS	ECP	Grade 1B	I
	Nonerythrodermic MF	ECP	Grade 2C	III

# of reported patients*: >300

	RCT	**CT**	**CS**	**CR**
Stage III (erythrodermic) MF + SS	1(8)	4 (64)	30(641)	1 (2)
Nonerythrodermic MF	1(8)	2 (18)	13(91)	0

MF = Mycosis fungoides; SS = Sézary syndrome

Description of the disease

Mycosis fungoides (MF) and its leukemic variant, Sézary syndrome (SS), account for 60 and 5% of cutaneous T cell lymphoma (CTCL) cases, respectively. Although MF and SS both involve clonal (malignant) epidermotropic CD3+/CD4+ T cells, gene and mRNA expression profile studies and immunophenotypic analyses suggest that they evolve through divergent pathological mechanisms. MF usually presents as recurrent, scaly skin patches and plaques (less commonly erythroderma) that may progress to papules or nodules, alopecia and erosions with lymph node and visceral organ infiltration. By comparison, SS presents with pruritic erythroderma, generalized lymphadenopathy, and with either $\geq 1 \times 10^9$/L circulating clonal CD4+ T cells (Sézary cells) or a CD4+/CD8+ cell ratio >10. Diagnosis and staging of MF/SS is based on a formal algorithm that incorporates clinical, histopathologic, molecular and immunopathologic criteria. Stage I includes skin patches and plaques (IA <10% body surface area[BSA] and IB ≥10%); II has either lymphadenopathy with low-grade pathological CD4+ T cell infiltration (IIA) or skin tumors (IIB); III has generalized erythroderma (≥80% BSA); and IV includes SS (IVA_1) and/or high-grade lymph node involvement (IVA_2) and/or visceral disease (IVB). Stage IA usually follows an indolent course without shortening life-expectancy. Patients with stages IB and IIA have median survivals exceeding 10–15 years whereas stages IIB, III and IV are "advanced-stage" with median survivals <5 years. Worse outcomes are observed with lower stage MF when >5% of peripheral blood lymphocytes are Sézary cells (i.e., B1 classification). Because advanced MF, SS and their treatments are associated with significant immune compromise, death can occur from infectious complications that often arise from skin lesions.

Current management/treatment

MF and SS are incurable. Therapy is aimed at alleviating symptoms, improving skin manifestations, controlling extracutaneous complications and minimizing immunosuppression. A number of consensus-based treatment recommendations for CTCL, MF and SS have been published by US and European consortia. In general, limited-stage disease (IA to IIA) typically responds to skin-directed therapies including topical corticosteroids, chemotherapy, retinoids, imiquimod, phototherapy (PUVA or UVB) and local radiotherapy. Generalized skin involvement can be treated with total skin electron beam therapy. Patients with B1 blood Sézary involvement, refractory limited- or more advanced-stage disease benefit from graduated intensities of systemic therapies using retinoids (bexarotene, all-trans retinoic acid), interferons, histone deacetylase inhibitors (vorinostat, romidepsin), the fusion toxin denileukin diftitox, systemic chemotherapy (methotrexate, liposomal doxorubicin, gemcitabine, pralatrexate, others), ECP and, for selected patients with progressive refractory disease, alemtuzumab or allogeneic stem cell transplantation. The United States Cutaneous Lymphoma Consortium (USCLC) recommends a stratified approach for SS. Primary intervention includes single or combined immunomodulatory therapies containing ECP, bexarotene, interferon-α, low-dose methotrexate and/or denileukin diftitiox, with or without adjunctive skin-directed therapies. Systemic chemotherapy is recommended for more aggressive SS, with consideration of alemtuzumab and stem cell transplantation for refractory disease.

Rationale for therapeutic apheresis

ECP involves the collection of circulating malignant CD4+ T cells, ex vivo treatment with 8-methoxypsoralen and UVA light and subsequent reinfusion of the treated cells. The therapeutic effect appears to be mediated by in vivo stimulation of anti-tumor immunity through the interactions of irradiated, apoptotic lymphoma cells with antigen-presenting dendritic cells. Aggregate clinical data of ECP monotherapy indicate that overall responses (ORs) of stage III (erythrodermic) MF and SS are roughly 36% and 25%, respectively, with 10% complete responses (CRs). Among the more than 100 reported patients with early-stage CTCL who were treated with ECP, OR rates ranged from 33–88% for monotherapy and 30–64% when ECP was combined with adjunctive therapies. A recent large retrospective study by Raphael et al., which included 98 patients with either stage IIIB MF (erythroderma + B1) or SS who were treated with ECP (median 28 treatments) plus another immunomodulatory agent, reported CRs and partial responses (PRs) in 30% and 45%, respectively. Response duration exceeded 12 and 24 months in 69% and 26%, respectively. Responses to ECP have been linked to short duration of disease, lower blood Sézary cell burden and significant early response of skin lesions (i.e., >50% regression within 6 months). The National Comprehensive Cancer Network (NCCN), UK Consensus panel and European Organization of Research and Treatement of Cancer (EORTC) recommend consideration of ECP as front-line therapy for stage III (erythrodermic) or IIIB (+B1) MF. Like USCLC, these groups also recommend ECP as an initial therapy option for SS with strong consideration of adjunctive skin-based or systemic therapies. ECP in combination with other nonchemotherapy systemic agents can be considered as a salvage approach for nonresponsive or relapsed patients or those with earlier stage disease and B1 blood involvement. The advantage of ECP is the relative lack of immune suppression and less risk of infections.

Technical notes

One cycle (two daily ECP procedures) once or twice per month yields comparable results to more frequent or intensive photopheresis regimens. For patients with SS, two monthly cycles have been recommended.

Volume treated: MNC product of 200–270 mL. The 2-process method collects and treats MNCs obtained from processing 2 TBV.
Replacement fluid: NA

Frequency: Two consecutive days (one cycle) every 2–4 weeks

Duration and discontinuation/number of procedures

The median time for a maximal response to ECP is 5–6 months although combination regimens may induce earlier remissions. Some patients may take as long as 10 months to respond. More rapid responses to ECP correlate with durability. Patients should be monitored and responses documented as per published guidelines. When maximal response is achieved with ECP, it can be reduced to one cycle every 6–12 weeks with subsequent discontinuation if no relapses occur. If MF/SS recurs, ECP can be reinstituted at once or twice monthly. If there is no response or disease progression after 3 months of ECP alone, combination therapy or alternate agents should be considered.

References [291–307]

*As of July 3, 2012 using Pub Med and journals published in the English language using the search terms cutaneous T-cell lymphoma, Sezary syndrome, extracorporeal photochemotherapy, and photopheresis. References of the identified articles were searched for additional cases and trials.

DERMATOMYOSITS/POLYMYOSITIS

Incidence: 1/100,000/yr	**Procedure**	**Recommendation**	**Category**
	TPE	Grade 2A	IV
	Leukocytapheresis	Grade 2A	IV

# of reported patients*: <100			
RCT	**CT**	**CS**	**CR**
1 (39)	0	0	0

DM = dermatomyositis; PM = polymyositis

Description of the disease

Dermatomyositis (DM)/polymyositis (PM) are forms of idiopathic inflammatory myopathy, with significant morbidity and mortality even with standard treatments. Muscle weakness, usually insidious at onset but worsening over time, is characteristic of both. Severity is variable. Elevation of muscle enzymes is present. Compared to PM, DM is associated with skin manifestations and cancer. With recent revisions in disease classification, fewer cases are labeled as PM. In addition, features may overlap with other connective tissue diseases.

Current management/treatment

The optimal therapeutic regimen remains unclear. Immunosuppressive and immunomodulatory treatments are commonly used to improve manifestations of the disease and allow reduction in corticosteroid dosing. Most patients respond to steroid therapy initially. Recurrent or resistant disease may require higher steroid doses, azathioprine, methotrexate, rituximab, or intravenous immune globulin.

Rationale for therapeutic apheresis

Autoantibodies such as ANA, anti-Ro, anti-La, anti-Sm, anti-ribonucleoprotein, or myositis-specific antibodies are commonly present. DM is considered an antibody/complement-mediated vasculopathy with immune complex deposition, including C5b-9 membrane attack complex deposition. In PM, muscle injury appears to be T-cell mediated, in which cytotoxic CD8+ T cells respond to an antigen on muscle fibers. In one randomized controlled trial (*Miller*), plasma exchange was no more effective in improving muscle strength or functional capacity (although serum levels of muscle enzymes improved) than sham apheresis.

References [308, 309]

*As of December 24, 2012 using PubMed and the MeSH search terms dermatomyositis, polymyositis, and inflammatory myopathies and plasmapheresis, plasma exchange.

DILATED CARDIOMYOPATHY, IDIOPATHIC

Incidence: 36/100,000/yr (US)	**Condition**	**Procedure**	**Recommendation**	**Category**
	NYHA II-IV	TPE	Grade 2C	III
	NYHA II-IV	IA	Grade 1B	II

# of reported patients*: >300				
	RCT	**CT**	**CS**	**CR**
TPE	0	0	1 (8)	2(2)
IA	3 (65)	10 (588)	14 (375)	1(1)

NYHA = New York Heart Association classification

Description of the disease

Dilated cardiomyopathy (DCM) is characterized by cardiac enlargement with impaired ventricular systolic function. Fifty percent of cases have no identifiable cause and are idiopathic (iDCM). iDCM is an uncommon cause of congestive heart failure, accounting for 15% of cases of heart failure in the elderly, it is responsible for half of heart transplants in the US. The pathogenesis of iDCM involves myocardial viral infection, inherited susceptibility factors, environmental variables, and immune variables. In up to 67% of patients with iDCM, viral genome can be detected on endomyocardial biopsy and 80% have cardiac autoantibodies.

Current management/treatment

iDCM is treated with angiotensin converting inhibitors, angiotensin receptor blockers, diuretics, digitalis, β-blockers, aldosterone antagonists, and vitamin K antagonists. Surgical management includes placement of a left ventricular assist device (LVAD) with the definitive therapy being cardiac transplantation.

Rationale for therapeutic apheresis

Autoantibodies to myocardial antigens are present in most patients. These can cause lysis, decrease contractility, and impair calcium transport of rat cardiomyocytes in bioassays. Immunization of rabbits with β1-adrenergic receptor extracellular domain and passive transfer of anti-troponin I antibodies to mice produce morphologic and clinical evidence of iDCM. It appears that the antibodies crosslink antigen targets and sarcolemmal Fc receptors inducing apoptosis and altering calcium transients. A study of explanted hearts demonstrated increased myocardial immunoglobulin in iDCM but not other causes of chronic cardiomyopathy. Treatment of iDCM with immunosuppression and/or IVIG has had mixed results.

Trials and case series using IA columns (i.e., sheep anti-human polyclonal antibody, Staphylococcal protein A agarose (SPAA), recombinant β1-adrenergic receptor extracellular domains, and tryptophan polyvinyl alcohol) have demonstrated short- and long-term improvement as measured by echocardiography, invasive monitoring, oxygen consumption, exercise tolerance, oxidative stress markers, BNP levels, and standardized symptom assessments. Histologic improvements include decreased myocardial HLA expression, inflammation, and desmin gene expression. A case series of 17 patients found decreased levels of cardiodepressant antibodies at 12 months compared to baseline. Another examining 10 patients found increased regulatory, decreased activated, and decreased costimulatory T cells 6 months after treatment. Improved function has been reported to last through the end of study follow-up, which has been 3–12 months after treatment. One series found left ventricular ejection fraction (LVEF) improvement in five of nine patients 3 years after a single course of IA. One controlled trial of 34 patients found persistent reduction in β1-adrenergic receptor antibodies and improved LVEF at 12 months with statistically significant differences in survival at 5 years between the treated group (82%) and matched controls (41%) ($P = 0.00071$). In addition to medical benefit, economic analysis found that the annual cost of treatment was less for those receiving IA despite the cost of the IA therapy. A controlled trial examined outcomes in 108 patients with β1-adrenergic receptor antibodies undergoing immunoadsorption compared to 55 patients with antibodies who did not undergo IA and 19 patients without antibodies who underwent IA. The probability of being cardiac transplant or LVAD free at 5 years was 69.4% for those who underwent IA treatment compared to 25.4% for those who did not ($P < 0.05$). Patients who underwent IA but who lacked β1-adrenergic receptor antibodies had a 47.4% probability of being cardiac transplant or LVAD free at 5 years ($P < 0.05$).

Most studies have examined patients with cardiac autoantibodies and some have only treated patients with antibodies to β1-adrenergic receptors. One series found improvement in all patients treated, even those without cardiac autoantibodies, while two controlled trials found only those with antibodies improved. One controlled trial examined only patients with cardiac antibodies and found only those with depressant antibodies improved. This heterogeneity may be related to autoantibody assays used.

Data from a case series of 8 patients treated with TPE has been published. Five of eight patients demonstrated a decline in myocardial IgG deposition at 6 months. A statistically significant improvement in LVEF and quality of life, measured with standardized symptom assessments, was seen at 3 and 6 months. TPE was also found to be effective in two patients with β1-adrenergic receptor antibodies treated with TPE due to the lack of available IA columns (one adult) and excessive extracorporeal volume of the IA device (one child).

In addition to the presence of cardiodepressant antibodies, other factors associated with response to therapy have included shorter duration of disease, the presence of low immunoglobulin affinity Fcγ-receptor IIa polymorphisms, and greater impairment of left ventricular function.

Technical notes

Studies have examined only patients with symptoms for >6 months optimally medically managed. Patients with iDCM due to inherited cytoskeletal abnormalities have not been treated and would not be expected to respond. Trials have used sheep anti-human immunoglobulin, SPAA, and β1-adrenergic receptor extracellular domain columns. Comparison of these found SPAA less effective due to a lower affinity for pathogenic IgG3 antibodies. Modified SPAA protocols with enhanced IgG3 removal were effective. Retrospective comparison of the modified SPAA protocol and protocols using the recombinant β1-adrenergic receptor extracellular domain columns found equivalent response to therapy. An analysis comparing outcomes in patients with β1-adrenergic receptor antibody using specific immunoadsorption versus nonspecific antibody removal found no difference in response or outcomes among the three IA columns examined (SPAA, recombinant β1-adrenergic receptor extracellular domain column, and immunoglobulin binding peptide column). IVIG (0.5 g/kg) was given after last apheresis treatment in the majority of IA studies and the TPE case series.

Volume treated: TPE: 1–1.5 TPV; IA: 2.5–5 L depending upon the saturation and regeneration characteristics of the column.
Replacement fluid: TPE: albumin; IA: NA

Frequency: TPE: Five treatments daily or every other day; IA: Various schedules: Most commonly 5 treatments daily or every other day

Duration and discontinuation/number of procedures

An IA trial comparing treatment with a single course of 5 consecutive days to 4 courses of 5 consecutive days repeated every four weeks failed to demonstrate differences in LVEF at 3 and 6 months between the two treatment schema. Repeat IA and TPE have been reported to be effective in patients experiencing increasing β1-adrenergic receptor antibody titers and/or worsening LVEF.

References [310–348]

*As of October 21, 2012 using PubMed and the MeSH search terms dilated cardiomyopathy and plasma exchange or plasmapheresis or immunosorbent technique or immunosorbent or immunoadsorption for articles published in the English language. References of the identified articles were searched for additional cases and trials. This fact sheet includes abstracts in the summary of published reports and considers them in determining the recommendation grade and category.

FAMILIAL HYPERCHOLESTEROLEMIA

Incidence: Heterozygotes: 200/100,000/yr; Homozygotes: 1/1,000,000/yr	**Condition**	**Procedure**	**Recommendation**	**Category**
	Homozygotes+	LDL apheresis	Grade 1A	I
	Heterozygotes	LDL apheresis	Grade 1A	II
	Homozygotes with small blood volume++	TPE	Grade 1C	II

# of reported patients*: >300

	RCT	**CT**	**CS**	**CR**
LDL apheresis	6 (228)	14 (277)	20 (333)	NA
TPE	0	1 (5)	14 (62)	NA

+Approved indications vary among countries, see technical notes below. ++Relative to manufacturers' recommendation for available selective removal devices.

Description of the disease

Familial hypercholesterolemia (FH) is an autosomal dominant disorder due to mutations of hepatocyte apolipoprotein-B (apo-B) receptors producing decreased hepatic LDL removal. FH exhibits gene dosage: Homozygotes (HM) exhibit cholesterol of 650–1,000 mg/dL, xanthomata by age 4 years, and death from coronary heart disease by age 20. Heterozygotes (HT) exhibit cholesterol 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, cholesterol adsorption blockers, nicotinic acid, and dietary modification can significantly reduce cholesterol. HMG-CoA reductase inhibitors lower LDL in HM and HT by only 10% and 25 to 49%, respectively. Progressive/unresponsive disease requires aggressive treatment such as distal ileal bypass, portacaval shunting, and liver transplantation. TPE was first used in 1975 with the subsequent development of selective removal systems to avoid loss of beneficial plasma components.

Rationale for therapeutic apheresis

A single treatment reduces LDL cholesterol levels by 65–70%. Short-term effects include improved myocardial and peripheral blood flow as well as endothelial function. LDL apheresis also alters atherogenic LDL subclass distribution, decreases apolipoprotein E4, and decreases adhesion molecule expression (VCAM-1, E-selectin, and ICAM-1). Because of the slow rise in LDL following treatment (1–2 weeks), the time-averaged cholesterol is reduced with repeated treatments. Long-term angiographic, ultrasound, 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 outcome studies have demonstrated significant reductions in coronary events.

Technical notes

Six selective removal systems are available. These are: (1) immunoadsorption: columns containing matrix bound sheep anti-apo-B antibodies, (2) dextran sulfate columns: remove apo-B lipoproteins from plasma by electrostatic interaction, (3) heparin extracorporeal LDL precipitation (HELP): precipitates apo-B 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 polyacrlyaminde beads, (5) dextran sulfate cellulose columns: same mechanism as column (2) but treats whole blood, and (6) membrane differential filtration: filters LDL from plasma. All have equivalent cholesterol reduction and side effects. Currently, the dextran sulfate plasma adsorption and HELP systems are cleared by the FDA.

Angiotensin converting enzyme (ACE) inhibitors are contraindicated in patients undergoing adsorption-based LDL apheresis. The columns function as a surface for plasma kallikrein generation, which converts bradykininogen to bradykinin. Kininase II inactivation of bradykinin is prevented by ACE inhibition resulting in unopposed bradykinin effect, hypotension and flushing. This is not seen with the HELP system.

Some LDL apheresis systems have been found to result in significant removal of vitamin B12, transferrin, and ferritin, which may cause anemia. Supplementation of vitamin B12 and iron may be necessary.

The goal is to reduce time-averaged total cholesterol >50% and LDL >60% from baseline. The time-averaged cholesterol can be calculated as follows: $C_{mean} = C_{min} + K(C_{max} - C_{min})$ where C_{mean} = the time-averaged cholesterol, C_{min} = the cholesterol level immediately after apheresis, K = the rebound coefficient, and C_{max} = the cholesterol level immediately prior to treatment. Values for K for FH HM and HT have been determined to be 0.65 and 0.71, respectively. To achieve these, reductions of total cholesterol of >65% or LDL of >70% must be achieved with each procedure. Numerous patient treatment criteria have been published. FDA criteria are: (1) functional HM with LDL >500 mg/dL (>13 mmol/L), (2) functional HT with no known cardiovascular disease but LDL >300 mg/dL (>7.8 mmol/L), and (3) functional HT with known cardiovascular disease and LDL >200 mg/dL (>5.2 mmol/L). The International Panel on Management of FH (Spain) indications are (1) FH HM and (2) HT with symptomatic coronary artery disease in whom LDL is >4.2 mmol/L (162 mg/dL) or decreases by <40% despite maximal medical management. The German Federal Committee of Physicians and Health Insurance Funds criteria are: (1) FH HM and (2) patients with severe hypercholesterolemia in whom maximal dietary and drug therapy for >1 year has failed to lower cholesterol sufficiently. The HEART-UK criteria are: (1) FH HM in whom LDL is reduced by <50% and/or >9 mmol/L (348 mg/dL) with drug therapy, (2) FH HT or a "bad family history" with objective evidence of coronary disease progression and LDL >5.0 mmol/L (193 mg/dL) or decreases by <40% despite drug therapy, and (3) progressive coronary artery disease, severe hypercholesterolemia, and Lp(a) >60 mg/dL (>3.3 mmol/L) in whom LDL remains elevated despite drug therapy (see fact sheet on lipoprotein (a) hyperlipoproteinemia). During pregnancy, LDL levels in individuals affected by FH can rise to extreme levels (1000 mg/dL (55 mmol/L)) that can compromise uteroplacental perfusion. There have been case reports of the use of LDL apheresis to allow for the successful completion of pregnancy.

TPE is effective but the availability of the selective removal systems and their superior efficacy in cholesterol removal makes its use uncommon. TPE may be the only option in small children where the extracorporeal volume of selective removal systems is too large. It has been recommended that apheresis begin by age 6 or 7 to prevent aortic stenosis that can occur in homozygous FH.

Volume treated: LDL apheresis: varies according to device; TPE: 1–1.5 TPV
Replacement fluid: LDL apheresis: NA; TPE: albumin

Frequency: Adjusted to reduce the time averaged LDL cholesterol by ≥60%, usually once every 1–2 weeks.

Duration and discontinuation/number of procedures

Treatment is continued indefinitely, adjusted to maintain the time-averaged cholesterol, as described.

References [349–466]

*As of October 21, 2012 using PubMed and the MeSH search terms hypercholesterolemia and apheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Incidence:	Condition	Procedure	Recommendation	Category
FSGS: 7/1,000,000	Recurrent in transplanted kidney	TPE	Grade 1B	I

# of reported patients*: 100–300

RCT	CT	CS	CR
0	3(48)	48(217)	14(16)

FSGS = focal segmental glomerulosclerosis

Description of the disease

Instead of a specific diagnosis, FSGS is a histologically characteristic finding in renal biopsies characterized by focal areas of sclerosis of some glomeruli adjacent to other intact glomeruli. Several FSGS histological variants (cellular, collapsing, tip lesion, perihilar, and not otherwise specified) have been described. FSGS variants appear to have different clinical presentations and treatment response, but podocyte injury and depletion are the central mediators for all FSGS. Approximately 80% of FSGS cases are primary (idiopathic). The causes of secondary FSGS include familial or genetic mutations in specific podocyte genes, drug-induced, and hemodynamic adaptive response. Idiopathic or primary FSGS is postulated to result from a plasma factor of unknown origin that injures the filtration barrier and/or increases glomerular permeability, and is present in some but not all patients with FSGS. This hypothesis is supported by the observation that FSGS may recur in a renal allograft. In one study, the majority of children with permeability factor had recurrence of FSGS. ESRD is expected in most patients with FSGS within 3–7 years, making transplantation a desirable option to avoid lifelong dialysis. Unfortunately, up to 40% of transplanted patients will experience a recurrence in the renal allograft. Idiopathic FSGS poses the highest risk of recurrence post-transplant. Clinical studies suggest that other risk factors for FSGS recurrence are younger age (6–15 years), short duration of native kidney disease (<3 years), history of recurrence with previous kidney transplant, heavy proteinuria in the period before transplantation, bilateral native nephrectomy, nonblack race, and kidney from a living donor. There are conflicting results in terms of gender as a risk factor for recurrence. FSGS recurrence can happen as early as a few hours post-transplant and as late as two years post-transplant. FSGS in the transplanted kidney is diagnosed histologically or when nephrotic range proteinuria develops in the post-operative period in patients with a history of FSGS in the native kidney or in a previous allograft. FSGS can also be suspected when patients with a history of FSGS have less severe but persistent proteinuria (> 0.5 g/day) within the first 10 days post-transplant. If not treated, FSGS will ultimately lead to permanent graft loss within months. Those who lose grafts to recurrent FSGS have >80% chance of developing the same lesion in subsequently transplanted kidneys.

Current management/treatment

The main goal of FSGS treatment is to achieve a complete or partial remission of proteinuria and prevent premature allograft loss. For secondary FSGS, underlying cause should be treated whenever possible. Patients with primary FSGS with proteinuria >3g/day do not benefit from TPE and should be candidates for corticosteroids, which remain its mainstay of treatment. Even though the use of TPE in treating FSGS in native kidneys has been disappointing, recurrent FSGS often responds to a combination of TPE, high dose corticosteroids, cyclosporine A or other immunosuppression like tacrolimus, cyclophosphamide, and/or an angiotensin II receptor antagonist (ARB) or an angiotensin-converting enzyme inhibitor (ACEI). More recently, rituximab, IVIG, and mycophenolate mofetil have also been used in conjunction with TPE.

Rationale for therapeutic apheresis

FSGS patients appear to have an ill-defined "permeability factor", probably a glycoprotein of molecular weight of 30–50 kDa capable of inducing profound leakage of albumin when incubated with isolated rat glomeruli. This factor has been shown to be removed by TPE and its decreasing plasma concentration coincides with improvement in proteinuria. Pretransplant TPE appears to prevent or delay recurrence in high-risk patients (*McCarthy*). More commonly, TPE is started once recurrence is diagnosed. The number of treatments needed to control proteinuria, surrogate marker of FSGS, is quite variable and can reach dozens. Garcia et al. treated 9 children with 10 TPE sessions plus high doses of cyclosporine, mycophenolate mofetil, and prednisone, starting <48 h after the diagnosis of proteinuria, and reported a 55% complete and 12% partial remission rates compared with no remissions among 5 children who did not receive TPE. In a study of adults in France, 8 of 9 patients achieved partial or complete remission of proteinuria with TPE but 5 still lost their grafts due to FSGS relapse. The authors concluded that the benefit of TPE is transient, especially if given as the sole immunosuppression. Valdivia et al. treated 7 adults with recurrent FSGS with 17 sessions of TPE exchanging a fixed volume of 2.5 L and reported that all patients had functioning grafts at an average of 10 months of follow-up. Sener et al. reported on 4 adults treated with 9–15 sessions of TPE and mycophenolate mophetil who had preserved renal function as late as 34 months after transplant. A recent retrospective study of adults with FSGS by Moroni et al. suggested that TPE and ACEIs resulted in either complete or partial remission of proteinuria in 80% of patients at the end of therapy. Tsagalis et al. reported 50% complete remission and 50% partial remission in 4 patients with recurrent FSGS treated with a combination of TPE and rituximab. Another trial by Canaud et al. reported 90% complete remission in 19 patients with recurrent FSGS treated with high-dose steroids, intravenous cyclosporine followed by oral cyclosporine and an intensive and prolonged course of TPE as compared to 27% of remission rate in 19 historic control patients. Some patients with recurrent FSGS have been treated with partial success with a combination of TPE and IA with staphylococcal protein A columns.

Technical notes

Vascular access may be obtained through arteriovenous fistulas or grafts used for dialysis.

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

Duration and discontinuation/number of procedures

One approach is to begin with 3 daily TPEs followed by at least six more TPEs in the subsequent 2 weeks, for a minimum of nine procedures. Another reported approach of intense/maintenance TPE treatment includes the following schedule: three per week for the first 3 weeks, followed by two TPE per week for 3 weeks, one TPE per week until month 3, 2 TPE per month until month 5, and once per month until month 9, but with concomitant immunosuppression treatment. Usually proteinuria decreases gradually while the patient is being treated with TPE as well as the creatinine, in those patients who showed decreased renal clearance at diagnosis of FSGS recurrence. 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 complete abolishment of proteinuria may take several weeks to months. Some patients require long-term regimens of weekly to monthly TPEs to prevent reappearance of the proteinuria. There are no clinical or laboratory characteristics that predict the likelihood of success with TPE. Although the optimum timing of initiating TPE has not been studied, it is recommended that TPE be instituted as soon as recurrent FSGS is diagnosed, in order to halt the process and maintain kidney function.

References [467–495]

*As of January 12, 2013 using PubMed and journals published in English language using the search terms FSGS, recurrent FSGS, plasmapheresis, and TPE. References of the identified articles were searched for additional cases and trials.

GRAFT-VERSUS-HOST DISEASE

Incidence:	Condition	Procedure	Recommendation	Category
Grade II – IV acute GVHD: 10–60%	Skin (chronic)	ECP	Grade 1B	II
moderate-severe chronic GVHD: 6–80%	Skin (acute)	ECP	Grade 1C	II
	Nonskin	ECP	Grade 2B	III

# of reported patients*: >300

	RCT	CT	CS	CR
Chronic skin	1 (95)	0	0	0
Acute/chronic skin + nonskin	0	2(41)	44(944)	9(13)

GVHD = graft-versus-host disease

Description of the disease

Graft-versus-host disease (GVHD) following allogeneic hematopoietic stem cell transplantation (HSCT) is classified as acute (aGVHD), chronic (cGVHD) or an overlap syndrome. "Classic" aGVHD occurs at ≤100 days after HSCT and is manifested as inflammatory tissue injury and necrosis with skin rash/desquamation, gastrointestinal (GI) tract epithelial inflammation and denudation with our without cholangiohepatic liver injury and cholestatic jaundice. "Late-onset" aGVHD, which occurs, recurs or persists at >100 days post transplant, has typical aGVHD manifestations without diagnostic clinical or histologic features of cGVHD. Classic cGVHD affects the skin, GI tract, liver, lungs, oropharynx, eyes, genital tract and/or musculoskeletal systems in the absence of aGVHD features. The "overlap syndrome" is the simultaneous presence of aGVHD with distinctive or diagnostic features of cGVHD. Acute GVHD results from activation of donor T-cells by host antigen-presenting cells (APCs), leading to T cell- and cytokine-mediated tissue injury. Chronic GVHD is due to dysregulated allo- or autoreactive T cells, B cells, APCs and natural killer (NK) cells leading to fibrosis, inflammation, sclerosis and atrophy of affected tissues. Detailed clinical assessment and severity scores have been developed to systematically grade GVHD subtypes. Severe GVHD that is unresponsive to treatment carries a high risk of death or severe morbidity due to end-organ complications and/or infections.

Current management/treatment

Acute GVHD of grades II to IV severity is routinely treated with a calcineurin inhibitor, systemic corticosteroids and, for GI disease, oral nonabsorbable corticosteroids. Roughly 50% of patients will not completely respond and may evolve to overlap syndrome. Antithymocyte globulin, anti-T cell or anti-cytokine antibodies, mycophenolate mofetil, sirolimus, pentostatin, mesenchymal stromal cells and ECP are salvage therapy options. Moderate to severe cGVHD is also managed with systemic immunosuppressive agents, including corticosteroids, calcineurin inhibitors, mycophenolate mofetil and/or sirolimus along with topical/local measures, as appropriate. Treatments for steroid-refractory or post transplant-dependent extensive cGVHD include azathioprine, pentostatin, monoclonal antibodies against T cells, B cells or cytokines, mesenchymal stromal cells and ECP. Persistent acute or chronic GVHD can lead to severe steroid side effects, infectious complications and progressive end-organ dysfunction.

Rationale for therapeutic apheresis

ECP involves the collection of peripheral blood leukocytes by apheresis, extracorporeal exposure of the leukocytes to 8-methoxypsoralen (8-MOP) followed by irradiation with ultraviolet A (UVA) light, and reinfusion of the photoactivated cells. The therapeutic effect of ECP for GVHD appears to be triggered by the ex vivo treated lymphocytes, which undergo apoptosis and modulate a number of in vivo immune responses. These include: increased dendritic cell differentiation; down regulation of autoreactive B cells; alterations in T helper subset populations and lymphocyte homing antigen display; a switch from pro-inflammatory to antiinflammatory cytokine production; and generation of regulatory T cells. A number of retrospective and prospective cohort studies using ECP for adults and children with GVHD have been reported. Overall response rates for steroid-refractory aGVHD reportedly range from 52–100%; with responses in skin, GI tract and liver ranging from 66–100%, 40–83%, and 27–71%, respectively. Complete responses and improved survival are often reported among aGVHD cohorts; however, the nonrandomized and retrospective results for ECP are not superior to results reported for alternative salvage approaches for steroid-refractory aGVHD. ECP is often not beneficial for patients with severe (grade IV) aGVHD. Roughly 30–65% of steroid-dependent patients with cGVHD improve with ECP; but most are partial responses. One study observed superior outcomes for patients with overlap or classic cGVHD as compared to patients with aGVHD subtypes. Skin, oral and ocular cGVHD manifestations respond in 30–100% of cases while liver, joint, and GI complications improve in 30–80%, 50% and 0–50%, respectively. ECP has also been reported to stabilize lung function with bronchiolitis obliterans syndrome related to cGVHD. Maximal responses for cGVHD usually require 2–6 months of treatment. But even without organ improvement, ECP may be beneficial as a corticosteroid-sparing modality. The single, randomized controlled trial using ECP for steroid-resistant skin cGVHD observed no statistically significant difference in total skin score at 12 weeks of ECP plus salvage GVHD therapy (n = 48) compared to salvage therapy alone (n = 47). However, unblinded assessments recorded 40% complete and partial responses at 12 weeks in the ECP-treated group compared to 10% in the non-ECP group ($P < 0.001$). More rapid skin improvement was also observed at weeks 12–24 of photopheresis and corticosteroids could be more quickly tapered. Among 29 control patients from this study who crossed over to receive 24 weeks of ECP for refractory disease, objective responses occurred in the skin and extracutaneous tissue in 33% and up to 70%, respectively. Clinical practice guidelines and consensus statements addressing the use of ECP for GVHD have been recently published by many groups. Collectively, these consider ECP as an established second-line therapy option for steroid-refractory cGVHD, particularly involving the skin. Some also recommend consideration of ECP as an adjunctive first-line modality for BOS and selected pediatric patients with aGVHD. The role of ECP for other GVHD subgroups remains undefined.

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 (UVAR XTS photopheresis system; Therakos Inc. Raritan, NJ). The Cellex instrument (Therakos) utilizes a continuous-flow system allowing treatment of patients ≥22 kg or smaller patients by incorporating a blood prime. Heparin is the conventional anticoagulant for Therakos instruments but ACD-A can be substituted if necessary. An alternative 2-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 MNC by standard continuous-flow apheresis, photoactivating the MNC by using a UVA light box (not approved in the US) and reinfusing the treated cells.

Volume treated: MNC product of 200–270 mL. The 2-process method collects and treats MNCs obtained from processing 2 TBV.
Replacement fluid: NA

Frequency: Two consecutive days (one cycle) every 1–2 weeks

Duration and discontinuation/number of procedures

For aGVHD, one cycle performed weekly until disease response and then tapered to every-other-week before discontinuation. For cGVHD one cycle weekly (or consider biweekly if treating only mucocutaneous cGVHD) until either a response or for 8–12 weeks, followed by a taper to every 2–4 weeks until maximal response.

References [296, 496–529]

*As of July 3, 2012 using PubMed and the MeSH search terms graft-versus-host disease, GVHD, extracorporeal photochemotherapy, photopheresis, for articles published in the English language. References of the identified articles were searched for additional cases and trials.

HEMATOPOIETIC STEM CELL TRANSPLANTATION, ABO INCOMPATIBLE

Incidence: 20–50% of allogeniec donor transplants	**Condition**	**Procedure**	**Recommendation**	**Category**
	Major HPC(M)	TPE	Grade 1B	II
	Major HPC(A)	TPE	Grade 2B	II
	Minor HPC(A)	RBC exchange	Grade 2C	III

# of reported patients*: >300

	RCT	**CT**	**CS**	**CR**
TPE (Major)	0	0	4(465)	10 (21)
RBC exchange (Minor)	0	0	2(24)	0

Hematopoietic progenitor cell (HPC), apheresis = HPC(A); HPC, marrow = HPC(M);Major = Major ABO incompatibility; Minor = Minor ABO incompatibility

Description of the disease

Major ABO incompatibility refers to the presence of natural antibodies in the recipient against the donor's A and/or B blood group antigens. These isoagglutinins may cause acute hemolysis of the red cells present in transplanted HPC products. Hematopoietic progenitor cell (HPC) products collected by apheresis [HPC(A)] contain a small amount of red cells (2–5% hematocrit) and therefore acute hemolytic signs/symptoms are uncommon, particularly if the total volume of incompatible red cells is <20 mL. By comparison, bone marrow HPC products [HPC(M)] contain 25–35% red cells and acute hemolytic reactions are a major concern when the recipient's isoagglutinin titer (IgG or IgM) is >16. Cryopreserved HPC products derived from cord blood may contain >20 mL of red cells but the A and B antigens are poorly developed in a newborn and most erythrocytes do not survive the freeze/thaw process. Thus, acute hemolysis is rare in this setting. After major ABO incompatible transplant, erythrocyte engraftment may be delayed in up to 20–30% of cases and some patients develop PRCA due to persistence of isoagglutinins that destroy donor erythroid precursors. Of note, pretransplant isoagglutinin titers are not predictive of the development of PRCA in this setting. In minor ABO incompatibility, plasma in the HPC donor product has antibodies against the recipient's A and/or B antigen. These products may induce acute hemolysis of recipient red cells if the donor isoagglutinin titer is high (i.e., >128) and infused plasma volume exceeds 200 mL (adult recipient). An additional risk with minor ABO incompatibility is development of delayed, severe and potentially fatal alloimmune hemolysis that typically occurs at 7–10 days post HPC infusion. This "passenger lymphocyte syndrome" (PLS) is caused by donor B lymphocytes that mount an antibody response against host A or B antigens. It is most common with HPC(A) products, which contain ten-fold more B cells than HPC(M), in blood group A recipients, after receipt of T cell depleted grafts and when post-transplant immunosuppression does not include methotrexate.

Current management/treatment

In major incompatibility, acute hemolytic transfusion reaction can be avoided by removing red cells from the HPC product or by reducing the recipient's isoagglutinin titer. The goal of RBC reduction, which may incur loss of HPCs, is based on institutional guidelines, which usually limit the total infusion of fresh donor red cells to 10–40 mL. In some European centers, recipient isoagglutinin reduction is accomplished by infusing donor-type red cells to adsorb antibodies in vivo. The more conventional approach is to perform TPE with the goal of reducing antidonor isoagglutinins to <32 prior to transplant. Although these interventions should prevent acute hemolysis, it is unpredictable whether they will prevent delayed red cell engraftment or avoid PRCA on a case-by-case basis. Management of post-transplant PRCA may include supportive care with transfusions, high-dose erythropoietin, TPE, IA, rituximab, donor lymphocyte infusions, discontinuation of cyclosporine, and antithymocyte globulin. In minor incompatible transplants with donor isoagglutinin titer >128 and HPC plasma volume >200 mL, product plasma reduction is performed to prevent recipient red cell hemolysis. Delayed, acute hemolysis (passenger lymphocyte syndrome) is usually unpredictable and is therefore managed expectantly with aggressive transfusion support or RBC exchange using group O erythrocytes. Two small, single-center studies have described using prophylactic automated red cell exchange to reduce the patient's residual erythrocytes to roughly 35% or below prior to transplantation. This approach was beneficial for selected patients who were felt to be at high risk for delayed severe hemolysis when treated on specific institutional protocols.

Rationale for therapeutic apheresis

For major incompatible transplant, TPE can be used as an alternative to red cell reduction in order to lower recipient anti-A and/or anti-B isoagglutinins and avoid manipulation of the HPC product. The recommended safety endpoint for TPE is recipient titers (both IgG and IgM) at 16 or below. The IgM isoagglutinins will be more effectively removed with TPE than IgG because IgG distributes into both intra- and extra-vascular compartments. In many studies, the pretransplant isoagglutinin titer was not predictive of the development of delayed engraftment or PRCA after major ABO incompatible transplant. However, a retrospective study of 153 major and bidirectional ABO incompatible transplant patients who underwent pretransplant isoagglutinin reduction by either transfusion of ABO incompatible donor type RBCs, TPE or a combination of the two reported significantly faster RBC engraftment ($P < 0.001$) and fewer cases of PRCA among treated patients, as compared to patients who received products that had undergone red cell reduction. For patients undergoing minor ABO incompatible transplantation, prophylactic red cell exchange can effectively reduce the number of host erythrocytes that would be the target of the PLS and severe, delayed hemolytic transfusion reaction. The published experience suggests that a pretransplant residual host red cell population of 35% or less can significantly mitigate delayed hemolysis in high risk patients. Severe, delayed hemolysis due to PLS has been anecdotally treated with TPE or RBC exchange to rapidly reduce isoagglutinin titer or replace host red cells with group O red cells, respectively.

Technical notes

TPE should be performed before infusion of major ABO incompatible HPC product, using albumin or combination of albumin and plasma compatible with both donor and recipient as replacement fluid. Automated RBC exchange replaces 1-1.5 patient's RBC volume with group O RBCs.

Volume treated: TPE: 1–2 TPV; RBC exchange: 1–1.5 RBC volumes **Frequency:** daily
Replacement fluid: TPE: albumin; donor and recipient ABO-compatible plasma; RBC exchange: group O RBCs

Duration and discontinuation/number of procedures

For major incompatibility the goal is to reduce the IgM or IgG antibody titers to <16 immediately before HPC transplantation If there is a delayed red cell recovery or PRCA, TPE may be performed (see fact sheet on PRCA). For high risk patients undergoing minor incompatible transplant, RBC exchange to 35% residual host erythrocytes.

References [530–539]

*As of October 1, 2012 using PubMed and the MeSH search terms ABO incompatible stem cell and bone marrow transplantation, plasmapheresis, plasma exchange, PRCA, RBC exchange for articles published in the English language. References of the identified articles were searched for additional cases and trials.

HEMOLYTIC UREMIC SYNDROME, ATYPICAL

Incidence: 3.3/1,000,000/yr (<18 yo); 7/1,000,000/yr (children in European community)	**Condition**	**Procedure**	**Recommendation**	**Category**
	Complement factor gene mutations	TPE	Grade 2C	II
	Factor H autoantibodies	TPE	Grade 2C	I
	MCP mutations	TPE	Grade 1C	IV

# of reported patients*: >300

	RCT	**CT**	**CS**	**CR**
Complement factor gene mutations	0	0	4(23)	21(26)
Factor H autoantibody	0	0	2(6)	2(2)

MCP = membrane cofactor protein

Description of the disease

HUS is characterized by a triad of Coombs negative microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury. The typical form of HUS follows a diarrheal (D+) prodrome and is associated with O157:H7 *E. coli* infections (see fact sheet on HUS). Atypical forms of HUS (aHUS), formerly referred to as D-HUS, are noninfection related and account for about 10% of cases. It is unrelated to diarrhea and can be sporadic or familial. The diagnosis of aHUS relies on (1) lack of associated disease, (2) no criteria for Shiga-toxin HUS (negative stool culture and PCR for Shiga toxin) and (3) no criteria for TTP (ADAMTS13 activity >10%). During the first year, 65% of all patients die, require dialysis, or have permanent kidney injury (*Mache*). aHUS has a prevalence of 1 in 100,000. Forty percent occur in young adults. The primary event in the pathogenesis of aHUS appears to be endothelial injury leading to formation of platelet-fibrin hyaline microthrombi which occlude arterioles and capillaries.

New insights indicate that aHUS is caused by uncontrolled activation of the alternative complement system. Complement-mediated thrombotic microangiopathy can manifest similar to HUS, but may have a chronic, progressive course, punctuated by catastrophic events such as retinal thrombosis, stroke, or acute kidney injury (*Mache*). Other reported complications of aHUS include liver involvement, pancreatitis, diarrhea, pulmonary hemorrhage, and peripheral thrombosis (*Noris*). Incomplete forms of aHUS, with mild or no typical hematologic features, may account for approximately 20% of aHUS cases. A growing list of genetic mutations and polymorphisms are now known to predispose to aHUS, primarily involving complement regulatory proteins, leading to complement-mediated endothelial injury. Approximately 60% of cases of aHUS involve the genes encoding complement regulators [factor H (*CFH*), membrane cofactor protein (*MCP*), and factor I (*CFI*)] or complement activators [factor B (*CFB*) and *C3*]. *CFH* mutations are the most frequent (20–30%). Five percent of aHUS is due to thrombomodulin mutations causing defective complement regulation. Acquired complement dysregulation has been reported in 6–10% of aHUS cases due to CFH autoantibodies. Penetrance of genetic forms of aHUS is around 50%. Other patients may have as yet unidentified complement mutations. Infection, pregnancy or drugs may trigger clinical disease in the presence of these mutations. A history of recurrent infections from Streptococcus or other encapsulated microorganisms such as *Neisseria meningitidis* or *Haemophilus influenza* should suggest a familial etiology. aHUS may present with an insidious onset at any age but many cases present in the first few months of life. It is characterized by marked hypertension, frequent relapses, end stage renal disease (ESRD), and mortality rate of 25%. In most cases of aHUS resulting from mutations in CFH and CFI, C4 levels are normal but C3 levels are low due to functional C3 deficiency (both are normal in MCP mutations). In familial aHUS, the lack of functional complement factors results in excessive activation of the alternate complement pathway causing glomerular injury. With the exception of infection-induced HUS, all children with HUS should be evaluated by measurement of *CFH, CFI, CFB, MCP, and C3* genetic testing and anti-CFH. However, because complement levels such as C3 and CFH proteins may be normal in many involved cases, they are not part of the initial diagnostic work-up.

Current management/treatment

Because treatment response is similar in patients with or without an identified genetic mutation, all patients diagnosed with aHUS should be treated immediately. TPE has been first line treatment for aHUS, although without prospective trials (*Loirat*). In contrast to older guidelines, empiric plasma therapy in all forms of aHUS is now recommended, pending genetic testing. Patients with MCP mutations do not require TPE as the factor does not circulate and plasma therapy has not shown to influence patient outcomes (*Saland*). The reported clinical response varies depending on the underlying genetic defect. In aHUS, plasma infusion can be initiated with 60–65 mL of plasma/kg/week followed by 20 mL of plasma kg/week as maintenance therapy. The European Group, based on expert consensus, recommends TPE be initiated urgently as it may be more effective than plasma infusion and up to 25% of children progress to ESRD in their first episode. Hematological remission is defined as a platelet count $>150 \times 10^9$/L for 2 weeks with no signs of hemolysis. Overall, 50–60% of patients with aHUS die or progress to ESRD requiring dialysis; some eventually undergo renal transplantation.

Rituximab may be initiated in aHUS due to CFH autoantibodies. More recently, eculizumab, the humanized anti-C5 monoclonal antibody that blocks activation of the terminal complement cascade, has been used for rescue therapy in plasma-resistant aHUS (*Dorresteijn, Norris*). In regulatory trials, eculizumab inhibited complement-mediated TMA and was effective in patients with and without identified genetic mutations. Both the FDA and the European Medicines Agency have added aHUS in pediatric and adult patients as indications for eculizumab. To date, reports indicate that 24 patients, including 11 children, have been treated off-label with eculizumab for overt aHUS episodes (*Zuber*); an additional 15 treated cases have been reported by the FDA and European agencies. Improved control of the disease over TPE is described in a number of cases.

Kidney transplantation may be required but risks recurrence of the disease process in the allograft, with graft loss common. Therefore the specific etiology must be pursued prior to transplantation. All candidates for renal transplantation must have genetic testing, as transplantation outcome may be related to mutation type. The risk of recurrence is negligible in patients with aHUS cases secondary to invasive *Strep pneumoniae* infection (see fact sheet on HUS, infection associated), drugs, or pregnancy, or those with MCP deficiencies. In contrast, high risk of recurrence persisting throughout life is present in patients with hereditary deficiencies, especially CFH and CFI mutations. aHUS leads to kidney graft failure in 60–90% of patients within one year. Correction of CFH or CFI deficiency and prevention of disease recurrence can be achieved with a combined liver and kidney transplant, since CFH and CFI are mostly hepatic in origin. However, this procedure is associated with high mortality rates, up to 50% (*Saland*). The alternative therapies may include use of purified complement factors or complement inhibitors. Eculizumab has recently been described pre-emptively to prevent recurrence in a kidney transplant. (*Nester*)

Rationale for therapeutic apheresis

The application of TPE as first-line therapy is largely based on anecdotal reports. The rationale is that it can effectively remove the autoantibody or mutated circulating complement regulators while replacing absent or defective complement regulators. Despite conflicting reports of the effectiveness, the European Group as well as others recommend TPE over plasma infusion because of potential therapeutic benefits of TPE without risk of volume overload, development of hyperproteinemia, or refractoriness to regular plasma infusion in a disease with the high risk of rapid progression to ESRD.

Technical notes

Since the majority of affected patients with aHUS are children, establishment of vascular access, RBC prime, and calcium supplementation are of special concern.

Volume treated: 1–1.5 TPV **Frequency:** Daily
Replacement fluid: Plasma; albumin (T activation associated HUS)

Duration and discontinuation/number of procedures

As there is no standardized approach, the duration and schedule of TPE for treatment of TTP have been empirically adopted to treat aHUS. European Group recommends that TPE be performed daily for 5 days after urgent initiation of TPE, 5 times per week for 2 weeks, then 3 times per week for 2 weeks with outcome evaluated at day 33 (*Sanchez*). These guidelines address neither continued treatment after initial therapy failure nor ongoing prophylactic treatment for patients with remission. As shown in a recent case series of three patients with *CFH* mutation, acute and prophylactic TPE in the pre- and post-renal transplant periods were effective in maintaining long-term native and allograft kidney function. Decisions of duration or to discontinue should be made based upon patient response and condition.

References [540–546]

*As of December, 20 2012 using PubMed and the MeSH search terms HUS, atypical HUS, plasmapheresis, and plasma exchange for articles published in the English language. References of the identified articles were searched for additional cases and trials.

HEMOLYTIC UREMIC SYNDROME, INFECTION ASSOCIATED

Incidence: D+HUS: 0.5–2/100,000 in general population	**Condition**	**Procedure**	**Recommendation**	**Category**
	STEC-HUS	TPE	Grade 1C	IV
	pHUS	TPE	Grade 2C	III

# of reported patients*: >300

	RCT	**CT**	**CS**	**CR**
D+HUS	1 (35)	1 (37)	52 (1365)	96 (110)

D+HUS = diarrhea-associated HUS; HUS = hemolytic uremic syndrome; pHUS = *Streptococus pneumonia* associated HUS; STEC-HUS = Shiga toxin-producing *Escherichia coli* associated HUS.

Description of the disease

HUS, pathologically a thrombotic microangiopathy (TMA), is characterized by the triad of nonimmune hemolytic anemia with red cell fragmentation, thrombocytopenia, and acute kidney injury. The platelet count that is diagnostic of HUS is $<150 \times 10^9$ (*Trachtman*); anemia and renal criteria vary. Distinguishing between HUS and TTP may be difficult at times; kidney failure is more dominant and ADAMTS13 activity more normal in HUS. The revised classification of TMA based on causation by the European Paediatric Research Group for HUS (referred as European Group) defines two subgroups of TMA: (1) that identified by well-defined etiology and (2) that recognized by a clinical association without clear etiology. The first subgroup includes HUS due to infection or complement dysregulation, TTP due to congenital or acquired ADAMTS13 deficiency, and TMA secondary to defective cobalamine metabolism or quinine. The second subgroup includes TMA associated with disorders such as HIV, malignancy, chemotherapy, ionizing radiation, calcineurin inhibitors, HSC or solid organ transplantation, pregnancy, SLE, antiphospholipid syndrome, glomerular disorders, etc. While the clinical presentation of HUS, TTP, and atypical HUS (aHUS) may overlap, molecular studies have identified three distinct causes: Shiga toxin (diarrhea-associated HUS (D+HUS) or typical HUS), ADAMTS 13 deficiency (TTP), and defects in complement regulation (aHUS).

Of infection-induced HUS, the most common form is D+HUS. Shiga toxin (STX)-producing *Escherichia coli* (STEC) remain the most common etiology of this illness, so that the label STEC-HUS is now substituted for D+HUS. D+HUS occurs 2–10 days after a prodrome of bloody diarrhea due to verocytotoxin (Shiga-like toxin)-producing bacteria, predominantly *E coli* O157:H7. Outbreaks and sporadic cases linked to other *E coli* serotypes (such as O111 and O26), enteric bacteria, or other microorganisms producing Shiga toxin continue to be reported. In most series, STEC enteritis leads to STEC-HUS in 5–15% of cases. It accounts for 85–90% of all HUS, can present in an epidemic fashion, occurs primarily in children >6 months, may affect all ages (particularly in epidemics), and has a favorable outcome with a mortality rate of <5%. In a systematic review of 49 studies from 18 countries published between 1950–2001 (*Garg*) 12% died or developed ESRD. In 2011, Europe experienced one of the largest recorded STEC-HUS outbreaks (at least 782 cases) due to a virulent and uncommon strain of *E coli* O104:H4. More than 1/5 of enterohemorrhagic cases developed STEC-HUS, with 54 deaths. Shiga toxins have proinflammatory and prothrombotic effects on the vascular endothelium and may attach to and stimulate endothelial cells to release "unusually large" von Willebrand factor (UL-vWf) multimers which activate and promote adhesion and aggregation of platelets. STX binds to multiple cells in the kidney and causes a spectrum of renal injury, including direct damage to glomerular endothelial cells and tubular epithelial cells. About a third of cases will require dialysis. Recurrent kidney injury may occur. Several findings point to activation of the alternate complement pathway in some STEC-HUS cases, although how is not clear. The other infection-induced HUS that usually occurs in children <2 years old is due to sepsis, pneumonia, or meningitis caused by *Streptococus pneumoniae* (pHUS). It has a mortality of 25% (19–50%). *S. pneumonia*, as well as other bacteria and viruses, produce a neuramidase which cleaves sialic acid residues from cell surface glycoprotein exposing the Thomsen-Freidenreich (T-) antigen. pHUS may occur by binding of naturally occurring IgM anti-T antibody to exposed T-antigen on erythrocytes, platelets and endothelium (*Petras*). Mortality rates are as high as 50%, significantly worse than STEC-HUS.

Current management/treatment

There is no compelling evidence from the available literature that TPE generally benefits patients with D+HUS, although patients with severe bloody diarrhea or neurological involvement may respond to timely TPE. The lack of general benefit was substantiated in an analysis of data on 298 adults generated from the 2011 outbreak in Germany (*Menne*). TPE was carried out in 84% yet evidence of benefit was not seen. However, in the recent European outbreak of D+HUS, early TPE appeared to ameliorate the course in five adults treated in Denmark (*Colic*). A retrospective study from France identified acute neurological involvement in D+HUS, half of whom responded to TPE (*Nathanson*). In the 2011 outbreak in Germany, IA was safely used to rapidly ameliorate severe neurological deficits in a prospective trial of 12 patients unresponsive to TPE or eculizumab (*Greinacher*). In children with infection induced-HUS, supportive care is the mainstay of therapy. Corticosteroids, plasma infusion or TPE have no proven role in D+HUS, although some children with severe *S. pneumoniae*-induced HUS may benefit from TPE (*Petras*). Preliminary experience with compassionate use eculizumab in the 2011 outbreak of STEC-HUS has been reported, with no definitive results.

Kidney transplantation may be required but risks recurrence of the disease process in the allograft, with graft loss common. Therefore the specific etiology must be pursued prior to transplantation. All candidates for renal transplantation must have genetic testing, as transplantation outcome may be related to mutation type. The risk of recurrence is negligible in patients with D+HUS.

Rationale for therapeutic apheresis

Shiga-toxin is a multisubunit AB5 protein complex. However, free Shiga-toxin has not been detected in the serum, and how it transits from the GI tract to target organs remains unclear (*Trachtman*). TPE could remove the toxin or factors that damage endothelium. For pHUS, TPE would remove antibodies directed against the exposed T-antigen, as well as circulating bacterial neuraminidase.

Technical notes

When TPE is performed in children with pHUS, avoidance of plasma-containing blood components is recommended to prevent the passive transfer of anti-T in normal plasma and possible polyagglutination due to T-activation. One longitudinal study of over 110 HUS/TTP patients has indicated that increased daily volumes of plasma may be associated with improved outcomes. (*Forzley*)

Volume treated: 1–1.5 TPV **Frequency:** Daily
Replacement fluid: STEC-HUS: plasma; pHUS: albumin

Duration and discontinuation/number of procedures

As there is no standardized approach, the duration and schedule of TPE for treatment of TTP have been empirically adopted to treat HUS. Decisions of duration or to discontinue should be made based upon patient response and condition.

References [547–554]

*As of December 20, 2012 using PubMed and the MeSH search terms HUS, plasmapheresis, and plasma exchange for articles published in the English language. References of the identified articles were searched for additional cases and trials.

HENOCH-SCHÖNLEIN PURPURA

Incidence: 13.5–22.1/100,000 with 1% developing RPGN	**Condition**	**Procedure**	**Recommendation**	**Category**
	Crescentic	TPE	Grade 2C	III
	Severe extrarenal manifestations	TPE	Grade 2C	III

# of reported patients*: <100			
RCT	**CT**	**CS**	**CR**
0	0	8 (65)	17 (20)

RPGN = rapidly progressive glomerulonephritis

Description of the disease

Henoch-Schönlein purpura (HSP) is the most common systemic vasculitis in childhood with 95% of cases occurring in this age group, but is less common in adults. Particularly in children, HSP is almost always a self-limiting disorder, unlike most other forms of vasculitis. It presents with arthralgia/arthritis, abdominal pain, kidney disease, and palpable purpura in the absence of thrombocytopenia or coagulopathy. Characteristically, it occurs following an upper respiratory tract infection. The highest incidence of HSP is in Caucasians while African Americans have the lowest incidence. HSP is a systemic small vessel vasculitis characterized by deposition of IgA-containing immune complexes within tissues. All patients develop palpable purpura. In the skin, these deposits lead to subepidermal hemorrhages and small vessel necrotizing vasculitis producing the purpura. One-quarter to one-half of cases involve the kidney, where IgA deposits within the mesangium of the glomerulus producing lesions ranging from mesangial proliferation to crescent formation and RPGN (see fact sheet on immune-complex RPGN). IgG autoantibodies directed at mesangial antigens may also play a role in pathogenesis. In other organs, necrotizing vasculitis leads to organ dysfunction or hemorrhage. Serum IgA levels were elevated in 60% of cases in one large adult series. Nonetheless, the precise role of IgA or antibodies to it in the pathogenesis of the disease remains unclear.

As stated, HSP can be self-limited, resolving spontaneously in 94% of pediatric patients. In adults, the clinical presentation is more severe and outcomes are worse. The presence of interstitial fibrosis and glomerulosclerosis on kidney biopsy, however, carries a poor prognosis. Reports of ESRD range from 15 to 30% over 15 years with additional cases advancing to stage IV chronic kidney disease. A small percentage of patients will develop significant extra-renal dysfunction including cerebritis or severe GI bleeding.

Current management/treatment

Treatment is predominantly supportive care including hydration, rest, and pain control. In patients with severe kidney involvement (i.e., crescentic glomerulonephritis) or severe symptoms of vasculitis, treatment also includes corticosteroids with or without immunosuppressants such as cyclophosphamide, azathioprine, or cyclosporine and IVIG. If ESRD develops, kidney transplantation may be necessary.

Rationale for therapeutic apheresis

The rationale for TPE is the removal of IgA-containing immune complexes or IgG autoantibodies. Early positive experiences of the use of TPE in treating some forms of RPGN resulted in the application of TPE to HSP when crescentic glomerulonephritis developed in the disease. In addition, because of the use of TPE to treat severe sequelae of other forms of vasculitis (see fact sheet on SLE), TPE has also been used to treat severe GI or skin manifestations and cerebritis in HSP.

Limited but encouraging data suggest TPE may benefit patients with severe disease. Seven case reports and eight case series totaling 67 patients have examined the use of TPE in treating RPGN in the setting of HSP. In 27 of these patients, concurrent immunosuppressive therapy was not given. In these patients treated with only TPE, 21 had complete resolution of their renal disease, two had persistent hematuria, one had persistent proteinuria, and two progressed to ESRD. The remaining patient was an adult who had resolution of renal disease with TPE but recurrence following discontinuation of TPE. The patient subsequently had complete resolution of renal disease with TPE and cyclophosphamide. Of the 40 patients treated with TPE and corticosteroids and/or immunosuppressants, all were reported to have had resolution of renal disease. In one case series, a single patient with HSP and decreased renal function without crescents was treated with TPE. This patient demonstrated no response to TPE.

Five case reports have examined the use of TPE in severe GI involvement in HSP unresponsive to corticosteroids and immunosuppressants. The GI involvement consisted of GI bleeding, prolonged ileus, or uncontrollable pain. In these reports, resolution of bleeding, ileus, or pain occurred following 1–4 TPE. In one case, resolution of pain occurred within 6 h of completion of TPE, but subsequently recurred. A total of nine TPE were performed in this patient, with resolution of pain after each, until there was no recurrence following the final TPE.

Three case reports and one case series, totaling six patients, have examined the use of TPE in treating cerebritis. Resolution of neurologic symptoms, including seizures, coma, and visual field disturbances, was reported to occur after one to two TPE.

Technical notes

Replacement fluid has varied depending upon the clinical situation with the final portion consisting of plasma in the presence of intracranial hemorrhage in cerebritis or GI bleeding. DFPP has also been used in a single patient with RPGN in HSP with resolution of renal disease.

Volume treated: 1–1.5 TPV	**Frequency:** 4–11 over 21 days
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

In cerebritis and severe GI manifestations, the course of therapy has ranged from one to six TPE daily with discontinuation of TPE upon resolution of symptoms. In RPGN, longer courses of therapy have occurred with therapy discontinued with improvement in renal function as determined by creatinine measurement.

References [555–576]

*As of October 21, 2012 using PubMed and the MeSH search terms plasma exchange or plasmapheresis and Henoch-Schönlein purpura for articles published in the English language. References of the identified articles were searched for additional cases and trials. This fact sheet includes abstracts in the summary of published reports and considers them in determining the recommendation grade and category.

HEPARIN INDUCED THROMBOCYTOPENIA

Incidence: 0.2–5% of patients exposed to heparin	**Condition**	**Procedure**	**Recommendation**	**Category**
	Pre-CPB	TPE	Grade 2C	III
	Thrombosis	TPE	Grade 2C	III

# of reported patients*: <100

	RCT	CT	CS	CR
Pre-CPB	0	0	2 (13)	3 (3)
Thrombosis	0	0	2 (48)	6 (6)

CPB = cardiopulmonary bypass

Description of the disease

Heparin induced thrombocytopenia and thrombosis is a major cause of morbidity and mortality in patients receiving heparin. Nonimmune heparin-associated thrombocytopenia (also called Type I heparin-induced thrombocytopenia) is characterized by a slight fall in platelet count within the first two days after heparin initiation, followed by normalization during continued heparin administration, and is without clinical consequences. The less common and more serious form, heparin-induced thrombocytopenia, type II (HIT-II) or "HIT" causes thrombocytopenia classically within 5–14 days of first exposure and can lead to life-or-limb threatening thrombosis. Antibodies specific for complexes of heparin and platelet factor 4 (PF4) are a hallmark of HIT. Thrombocytopenia with HIT typically represents <50% reduction from the pretreatment platelet count with a nadir above 20 x 10^9/L and is only rarely associated with bleeding. Use of unfractionated heparin (UFH) as compared to low molecular-weight heparin (LMWH), surgical (vs. medical) patients and female gender are associated with greater risk for the development of HIT. Delayed-onset HIT can occur in patients after heparin has been withdrawn and this can be a diagnostic dilemma and therapeutically challenging. Individuals who have persistent HIT antibodies after exposure to heparin within the preceding 100 days may rapidly (<48 h) develop thrombocytopenia (within 24 h) after heparin re-exposure.

Current management/treatment

After recognizing a possible case of HIT, all heparins, including LMWH, should be discontinued. Because of the continued risk of thrombosis after heparin cessation, all patients with confirmed HIT are therapeutically anticoagulated with an alternative agent, typically a direct thrombin inhibitor (DTI) or fondaparinux (off-label use). The duration of anticoagulation is based on whether the patient has pre-existing thrombosis (as the original indication for heparin), new HIT-associated thrombosis or no associated thrombosis. Anticoagulation can be transitioned to warfarin after normalization of the platelet count. HIT management is particularly challenging in two scenarios: (1) Worsening or new thrombosis with life- or-limb-threatening complications (e.g., ischemia of extremities due to thrombosis or recurrent, massive pulmonary embolism) despite optimal management with nonheparin anticoagulants; and (2) Persistent HIT antibodies in patients who need cardiac surgery on cardiopulmonary bypass (CPB). The standard anticoagulant used with CPB is UFH due to its short half-life, and immediate reversibility (with protamine); however, heparin is contraindicated with active HIT or persistent HIT antibodies even without thrombocytopenia. Consensus guidelines recommend the use of bivalirudin over other nonheparin anticoagulants and over heparin plus antiplatelet agents. The major concern with DTI use during CPB is severe bleeding.

Rationale for therapeutic apheresis

In the setting of CPB with a prior history of HIT but no detectable HIT antibodies, brief UFH anticoagulation during CPB is usually well tolerated without adverse sequelae. In the setting of urgent need for surgery during active HIT, or with persistent HIT antibodies, TPE can be considered as an alternative to using a DTI during CPB. In the largest retrospective series on the use of TPE in the pre-CPB setting, a single TPE treatment reduced HIT antibody titers (measured by PF4-polyvinylsulfonate ELISA) to negative (<0.4 OD) in 6 of 9 patients and significantly decreased titers in the other 3 patients (decreased 48–78%). None of the 9 patients developed clinical HIT after CPB with UFH; however, one patient developed an ischemic foot in the setting of cardiogenic shock which was not thought to be HIT-related. TPE has also been used in the setting of life- or-limb-threatening new or progressive thrombosis in HIT patients. In the largest study of TPE in HIT patients with arterial or venous thrombosis and >50% drop in platelet count, three experimental patient groups were compared: (a) Those who did not receive TPE ($n = 16$); (b) those who received TPE within 4 days of onset of thrombocytopenia ("early" group; $n = 21$); and (c) those who received TPE 4 days or later after onset ("late" group; $n = 7$). Information on use of alternative anticoagulants in these patients was not provided. Reduction in HIT antibody levels was quantitated by optical density in a PF4-heparin ELISA in some patients and with heparin-induced platelet aggregation (HIPA) testing in others. Two TPE treatments were performed (1–1.5 PV) 24–48 h apart which resulted in a negative HIPA test in greater that three-fourths of all patients. The 30-day mortality rate was 4.8, 57, and 32% in the early, late and control groups, respectively. Platelet recovery time, incidence of thrombotic events, and length of hospital stay were similar in the early group and controls, but were higher in the late group. Cause of death was not discussed in this report. Several other case reports also document use of TPE in the setting of life-or-limb threatening thrombosis. TPE protocols used in this setting have been heterogeneous (1–5 treatments) and have utilized different laboratory tests for serological monitoring of the HIT antibody (ELISA, HIPA) to optimize treatment regimen. Some of these case reports have utilized TPE in conjunction with non-UFH anticoagulation while others have used TPE alone.

Technical notes

Because a high percentage of cardiac surgery patients have heparin-PF4 directed antibodies by ELISA (a highly sensitive but relatively nonspecific assay), the diagnosis of HIT must be based upon high clinical suspicion as determined by one of two scoring systems (4T score or the HEP score). A confirmatory functional platelet activation assay, the serotonin release assay (SRA) may be helpful in the complex patient. In the absence of access to the SRA assay, the potential risks and benefits of performing TPE followed by intraoperative heparin use in place of UFH alone (without pre-CPB TPE) or alternative anticoagulation should involve a careful evaluation of the HIT score and results of HIT testing (e.g., ELISA/HIPA). If TPE is utilized, the laboratory must be able to reliably quantitate the HIT antibody titer as a guide to TPE efficacy (as outlined below).

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

Duration and discontinuation/number of procedures

In the setting of CPB, TPE has typically been used preoperatively until HIT antibody titers become negative by the testing method used. In the setting of thrombosis, the number of procedures performed in clinical reports has been guided by clinical response (e.g., resolution of thrombosis-related tissue ischemia) and reduction in HIT antibodies levels with TPE (conversion of positive to negative result in the HIT assay).

References [172, 577–610]

*As of October 2, 2012 using PubMed and the MeSH search terms heparin induced thrombocytopenia/thrombosis, plasma exchange, plasmapheresis and cardiopulmonary bypass for articles published in the English language. References of the identified articles were searched for additional cases and trials.

HEREDITARY HEMOCHROMATOSIS

Incidence: 1.4/100,000/yr	**Procedure** Erythrocytapheresis	**Recommendation** Grade 1B	**Category** I
# of reported patients*: 100–300			
RCT	**CT**	**CS**	**CR**
1 (38)	0	13 (122)	0

Description of the disease

Hereditary hemochromatosis includes a number of inherited disorders that result in iron deposition in the liver, heart, pancreas and other organs. The genetic mutation, accounting for >90% of cases (and almost all cases in Caucasians of Northern European ancestry) is homozygosity for a single missense mutation in the *HFE* gene on chromosome 6p21 that results in substitution of cysteine with tyrosine at amino acid 282 and is referred to as the C282Y mutation. The prevalence of *HFE* hemochromatosis is approximately 1:200 among Caucasians. Abnormalities of the *HFE* gene may result in a defect in iron sensing in the deep crypt cells of gut epithelium and thus inappropriate iron uptake despite abundant iron stores in the body. Other mutations in genes coding for hemojuvelin, hepcidin, transferrin receptors or ferroportin, have been described in rare families with non-HFE syndromes of hereditary hemochromatosis. In *HFE* hemochromatosis, iron accumulation can ultimately result in liver failure (cirrhosis, hepatocellular carcinoma), diabetes, hypogonadism, hypopituitarism, arthropathy, cardiomyopathy and skin pigmentation. Diagnosis is suggested by a persistent serum transferrin saturation of $\geq$45% and/or unexplained serum ferritin of $\geq$300 ng/mL in men or $\geq$200 ng/ml in premenopausal woman. The clinical penetrance of disease is variable, with only 70% of homozygotes developing clinical manifestations of disease, only 10% showing any end-organ complications and roughly 0.04% showing full-blown complications of disease.

Current management/treatment

Because hereditary hemochromatosis is a disease of iron overload, iron removal by therapeutic phlebotomy has been the mainstay of treatment. Phlebotomy therapy is recommended when serum ferritin is elevated even in the absence of symptoms or signs of end-organ damage. Typically, 1 unit of whole blood is removed weekly or biweekly until the serum ferritin is <50 ng/mL without resultant anemia. Patients with tissue complications of hemochromatosis usually have a ferritin >1000 ng/mL and typically present with upward of 20 g of excess iron. Thus, with 250 mg of iron removed per phlebotomy, two years may be needed to achieve therapeutic iron depletion. Thereafter 2–4 phlebotomies per year are usually adequate to maintain the ferritin $\leq$50 ng/mL. Malaise, weakness, fatigability and liver transaminase elevations often improve during the first several weeks of treatment, but joint symptoms may initially worsen before eventually improving (if at all). Cardiomyopathy and cardiac arrhythmias may resolve with phlebotomy, but insulin-dependent diabetes generally will not. The risk of hepatocellular carcinoma correlates strongly with cirrhosis and persists despite iron depletion. In patients therapeutic phlebotomy is contradicted, iron chelation can be used as an alternative treatment, although it is costly and has side effects.

Rationale for therapeutic apheresis

Automated erythrocytapheresis removes erythrocytes only rather than whole blood and each procedure can remove two to three times that amount of RBCs and iron while maintaining isovolemia. In a prospective trial, erythrocytapheresis with removal of a maximum of 800 mL of red cells could be performed every 2–4 weeks while maintaining the starting hematocrit (Hct) at $\geq$36% and post-procedure Hct at $\geq$36%. Using this approach, (mean $\pm$ SD) 565.5 $\pm$ 152 mL of red cells was removed with each procedure resulting in removal of 878 $\pm$ 315 mg of iron per month. The serum ferritin was reduced from 1517 $\pm$ 1329 ng/mL to 20 $\pm$ 6.5 ng/mL after 6.7 $\pm$ 2.9 months and 13.5 $\pm$ 7.2 apheresis sessions. A similar protocol was used in a pilot study from the Netherlands in which six patients achieved iron depletion with erythrocytapheresis in a mean [range]) of 9.8 [6–18] procedures over 4.8 [2–9] months, compared to 32 [22–48] procedures over 15.5 [10–24] months required for phlebotomy among six historical control patients. A follow-up prospective, randomized trial by this same group compared erythrocytapheresis of 350–800 mL of erythrocytes every 2 weeks to a minimum post procedure Hct of $\geq$30% with weekly phlebotomy of 500 mL among 38 patients with newly diagnosed C282Y-positive hereditary hemochromatosis. Primary outcome measures were the duration and number of treatments to reach ferritin $\leq$50 ng/mL. Secondary outcome measures were decline in hemoglobin during treatment, improvement in liver function, patient discomfort and cost. Each erythrocytapheresis procedure removed more than twice the volume of erythrocytes and ~2-fold more iron than a single phlebotomy procedure without inducing symptomatic anemia. The mean number of procedures and treatment duration to achieve ferritin of $\leq$50 ng/mL were 9 and 20 weeks for the erythrocytapheresis group versus 27 and 34 weeks, respectively, for the phlebotomy group. Both outcomes were statistically significantly different in favor of erythroctyapheresis. No difference in adverse events and no significant difference in total treatment costs were observed between the erythrocytapheresis and phlebotomy groups (the higher cost of erythrocytapheresis was offset by a significant reduction in lost work productivity due to phlebotomy visits).

Technical notes

While reported methods vary, the Dutch trial employed a schedule of erythrocytapheresis of 350–800 mL of erythrocytes every 2 weeks. The preprocedure hemoglobin should be $\geq$12 mg/dL or Hct $\geq$34%. An interval of 3 weeks may be required, especially for women to avoid a postprocedure Hct <30%. The actual volume of erythrocytes to be removed (VR) with each procedure can be calculated as:

VR = [(starting HCT − target HCT) ÷ 79] × [blood volume (mL/kg) × body weight (kg)].

Volume treated: Erythrocytapheresis of up to 800 mL of RBCs **Replacement fluid**: Replace at least $^1/_3$–$^1/_2$ of removed RBC volume with saline	**Frequency:** Every 2–3 weeks, keeping the preprocedure Hct $\geq$34% and postprocedure Hct $\geq$30%

Duration and discontinuation/number of procedures:

Erythrocytapheresis every 2–3 weeks, or as tolerated, until serum ferritin <50 ng/mL. Maintenance treatment can follow with infrequent therapeutic phlebotomy or erythrocytapheresis.

References [611–625]

*As of July 9, 2012 using PubMed and the MeSH search terms hemochromatosis and apheresis for journals published in the English language. References of the identified articles were searched for additional cases and trials.

HYPERLEUKOCYTOSIS

Incidence: AML: WBC $>100 \times 10^9$/L: 5–18% in adults, 12–18% in children; ALL: WBC $>400 \times 10^9$/L: $\leq 3\%$	**Condition**	**Procedure**	**Recommendation**	**Category**
	Leukostasis	Leukocytapheresis	Grade 1B	I
	Prophylaxis	Leukocytapheresis	Grade 2C	III

# of reported patients*: >300

	RCT	**CT**	**CS**	**CR**
AML	0	5 (385)	7 (199)	10 (12)
ALL	0	3 (366)	3 (39)	1 (1)

Description of the disease

Hyperleukocytosis is defined as a circulating white blood cell (WBC) or leukemic blast cell count $>100 \times 10^9$/L. Hyperleukocytosis with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) may be associated with tumor lysis syndrome (TLS), disseminated intravascular coagulopathy (DIC), leukostasis and worse prognosis. Leukostasis refers to end-organ complications due to microvascular leukoaggregates, hyperviscosity, tissue ischemia, infarction and hemorrhage that are not attributable to infectious, thromboembolic or other underlying etiologies. Leukostasis pathogenesis relates to cell rigidity, size, rheological properties and cytoadhesive interactions. Compared to lymphoid blasts, myeloid blasts are larger, less deformable and their cytokine products are more prone to activate inflammation and endothelial cell adhesion molecule expression. Leukostasis in AML usually occurs with WBC counts $>100 \times 10^9$/L and in ALL with WBC counts $>400 \times 10^9$/L. The monoblastic/monocytic variants of AML (i.e., M4 and M5) are particularly susceptible to leukostasis complications and may occur at blast counts $<50 \times 10^9$/L. CNS manifestations include confusion, somnolence, dizziness, headache, delirium, coma, and parenchymal hemorrhage. Pulmonary complications include hypoxemia, diffuse alveolar hemorrhage (DAH) and respiratory failure with interstitial and/or alveolar infiltrates. A leukostasis clinical grading scale has been developed, with greatest risk related to severe pulmonary, neurological and other end-organ manifestations and M4/M5 AML subtypes. Notably, age, high lactate dehydrogenase (LDH) and WBC counts are not predictive of poor outcome. Although hyperleukocytosis in AML is associated with a 2- to 3-fold higher early mortality rate the relative benefits of rapid cytoreduction by leukocytapheresis versus aggressive chemotherapy and supportive care alone, remain undefined. Leukostasis complications with other leukemias are rare but may occur with chronic myelomonocytic leukemia and WBC counts $>100 \times 10^9$/L with high LDH. Priapism may occur with chronic phase chronic myeloid leukemia and WBC; suggesting counts $>500 \times 10^9$/L.

Current management/treatment

Definitive treatment of hyperleukocytosis in AML or ALL involves induction chemotherapy with aggressive supportive care. Hydroxyurea and/or cytarabine are useful temporizing cytoreductive agents for AML. Hyperuricemia and TLS are treated with intravenous fluids, electrolyte replacement, allopurinol or rasburicase, alkalinization of the urine and dialysis. Bleeding and coagulopathy are managed with plasma, cryoprecipitate and/or platelet transfusions. Red cell transfusions should be deferred, however, to avoid augmenting hyperviscosity and inducing leukostasis. Rapid cytoreduction is indicated to treat symptomatic leukostasis. Adjunctive radiation therapy may be considered with parenchymal brain lesions. Prophylactic cranial irradiation is not indicated. Adjunctive dexamethasone has been proposed for lung injury with M5 AML; however, this intervention has not been studied in a controlled trial.

Rationale for therapeutic apheresis

Multiple retrospective cohort studies of AML with hyperleukocytosis suggest that prophylactic leukocytapheresis (i.e., without leukostasis complications) can reduce the rate of early death (i.e., at ≤ 3 weeks into treatment); although there is no impact on later mortality and overall or long-term survival. One cohort study showed that a postprocedure WBC count of around 90×10^9/L was not predictive of one-week survival, however, and suggested that either a lower WBC count may be needed and/or that associated comorbidities are more important determinants of outcome. A second cohort study also found no decrease in early mortality and raised concerns that leukocytapheresis might delay starting chemotherapy. Despite the inability to predict the onset of leukostasis complications and lack of a clear treatment goal, prophylactic leukocytapheresis is a reasonable consideration for selected AML patients with rapidly rising blast counts $>100 \times 10^9$/L, especially with the M4/M5 subtypes. Among children and adults with ALL, clinical symptoms of leukostasis develop in <10% at WBC counts $<400 \times 10^9$/L. Therefore, prophylactic leukocytapheresis offers no advantage over aggressive induction chemotherapy and supportive care, including those with TLS. By comparison, pulmonary and CNS complications develop in over 50% of children with ALL and WBC counts $\geq 400 \times 10^9$/L, suggesting that prophylactic leukocytapheresis might be beneficial in that setting. The category III indication for leukocytapheresis as prophylaxis reflects the limited and conflicting data available in the literature. For ALL or AML with clinical leukostasis, numerous reports describe rapid reversal of pulmonary and CNS manifestations after cytoreduction with leukocytapheresis. Improvement may not be observed, however, if severe end-organ injury or hemorrhage has already occurred. A recent retrospective survey of leukocytapheresis plus chemotherapy for clinical leukostasis in 15 patients with AML, including 7 with M4 or M5 subtypes, observed a 7-day mortality rate of 46% and only 2 30-day survivors. Notably, the postapheresis goal of WBC count $<100 \times 10^9$/L was not reached in most cases, again raising speculation that a more aggressive treatment endpoint might be necessary. In symptomatic patients, leukocytapheresis should be repeated until clinical manifestations resolve or a maximum benefit is achieved. Chemotherapy should not be postponed and is required 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 for AML or ALL. Red cell priming may be employed for selected adults with severe anemia; however, undiluted packed RBCs should be avoided in small children with hyperviscosity. Utilize replacement fluid to ensure at least a net even ending fluid balance of $\pm 15\%$ of total blood volume (TBV). The collect rate at the start and during the procedure should be carefully adjusted and monitored to optimize WBC removal and ensure safety.

Volume treated: 1.5–2 TBV **Frequency:** Daily; twice-daily for life-threatening cases
Replacement fluid: Crystalloid, albumin

Duration and discontinuation/number of procedures

For prophylaxis of asymptomatic AML patients, discontinue treatments when the blast cell count is $<100 \times 10^9$/L (closely monitor patients with M4 and M5 subtypes). For AML patients with leukostasis complications, discontinue when the blast cell count is <50 to 100×10^9/L and clinical manifestations are resolved. For prophylaxis of asymptomatic ALL patients, discontinue treatment when the blast cell count is $<400 \times 10^9$/L; and for those with leukostasis complications, when the blast cell count is $<400 \times 10^9$/L and the clinical manifestations have resolved.

References [626–655]

*As of July 3, 2012 using PubMed and the MeSH search terms hyperleukocytosis, leukostasis, apheresis, leukapheresis, leukocytapheresis and acute leukemia for reports published in the English language. References of the identified articles were searched for additional cases and trials.

HYPERTRIGLYCERIDEMIC PANCREATITIS

Incidence: 18/100,000/yr	**Procedure** TPE	**Recommendation** Grade 2C	**Category** III
# of reported patients*:100–300			
RCT	**CT**	**CS**	**CR**
0	1 (29)	12 (132)	33 (33)

Description of the disease

Hypertriglyceridemia (HTG) results from elevations in the lipoproteins responsible for triglyceride (TG) transport. Primary causes (less than 10% of cases) include mutations/polymorphisms in genes such as those encoding lipoprotein lipase (LPL) and its activator apo C-II. Secondary causes include diabetes mellitus (DM), chronic renal failure, nephrotic syndrome, hypothyroidism, pregnancy, lack of exercise, high-carbohydrate diets, excess alcohol intake, and medications such as corticosteroids, estrogens, retinoids, diuretics, and antiretroviral. 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 >500–1,000 mg/dL. These include acute pancreatitis, chronic abdominal pain, hepatosplenomegaly, eruptive xanthomas, lipemia retinalis, peripheral neuropathy, memory loss/dementia, and dyspnea. Endothelial damage due to chemical irritation by fatty acids and lysolecithin is felt to cause pancreatitis while hyperviscosity and tissue deposition produce the other complications.

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

Current management/treatment

Treatment for HTG 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 46–80% have been reported with improvement in symptoms of pancreatitis following one to three TPE procedures. The single trial (with historic control) by Chen et al., however, found no difference between standard therapy (ST) and TPE ($n = 10$) versus ST alone ($n = 19$) in patients with severe acute pancreatitis with regard to mortality, systemic complications, and local complications in patients with severe pancreatitis. 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.

Eight case reports examined TPE use in pregnant women with HTG-induced pancreatitis. In six cases, TPE was performed due to the presence of pancreatitis. The number of treatments ranged from 1 to 10 (median 2) with Cesarean section due to fetal distress and delivery of a preterm infant occurring in 5 of 6 cases. Since fibrate, the mainstay of medical therapy for HTG, has been associated with teratogenic effects, TPE had been used as an alternative prevention and treatment strategy during pregnancy. In two additional cases, patients were treated prophylactically because of a history of pancreatitis. TPE was performed 6 and 13 times beginning at 25 and 19 weeks gestation, respectively. In both cases, healthy infants were delivered at 34 weeks. In one of these cases, treatment was determined by TG levels with a goal to maintain a TG below 1,000 mg/dL.

Two case reports have examined TPE in generalized lipoatrophy. 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, including amenorrhea, galactorrhea, proliferative retinopathy, and hypertension which were attributed to the treatment. The authors did not recommend TPE because of these findings. It should be noted that these complications have not been reported as complications of TPE and are therefore of questionable association.

Other causes of HTG pancreatitis which have been reported to be treated by TPE include HTG due to medications such as isotretinoin, ritonavir, cyclosporine, and asparaginase as well as case report of lipid emulsion over-dose in a patient on TPN. In all of these cases, treatment has been reported to be beneficial.

Two series have reported chronic TPE treatment in a total of 8 patients with recurring pancreatitis. Both series reported TPE reduced or prevented further episodes of pancreatitis. In the larger of the series (6 patients), the frequency of pancreatitis was reduced by 67%. Treatments were done at a frequency to maintain the TG levels below 150 mg/dL.

It is important to note that TPE can be effective to rapidly decrease the TG level, its effect is transient; adequate lipid lowering treatment is essential to achieve the persistent effect.

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 though some authors have recommended its use only if there is no improvement with standard therapy.

Volume treated: 1–1.5 TPV	**Frequency:** Therapeutic: daily for 1–3 days depending upon patient course and TG level
Replacement fluid: Albumin, plasma	

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 additional treatments if necessary. For patients treated prophylactically, chronic therapy for years has been reported.

References [656–665]

*As of June 4, 2012 using PubMed and the MeSH search terms plasma exchange or plasmapheresis and hypertriglyceridemia and pancreatitis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

HYPERVISCOSITY IN MONOCLONAL GAMMOPATHIES

Incidence: 5/1,000,000/yr	**Condition**	**Procedure**	**Recommendation**	**Category**
	Symptomatic	TPE	Grade 1B	I
	Prophylaxis for rituximab	TPE	Grade 1C	I

# of reported patients*: >300

	RCT	**CT**	**CS**	**CR**
Symptomatic	0	3 (46)	18 (253)	12 (12)
Prophylaxis for rituximab	0	0	3 (45)	2(2)

Description of the disease

Whole blood viscosity varies as a function of hematocrit, RBC aggregation, plasma proteins, and interactions between the blood and the blood vessel wall. 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 caused by this altered physiology. Specific signs and symptoms include headache, dizziness, vertigo, nystagmus, hearing loss, visual impairment (retinal hemorrhage/detachment), somnolence, coma, and seizures. Other manifestations include congestive heart failure (related to plasma volume overexpansion), respiratory compromise, coagulation abnormalities, anemia, fatigue (perhaps related to anemia), peripheral polyneuropathy (depending on the specific properties of the immunoglobulin), and anorexia. This syndrome occurs most typically in Waldenström's macroglobulinemia, a lymphoplasmacytic lymphoma associated with the elaboration of $\geq$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 $\geq$6–7 g/dL of monoclonal IgA or $\geq$4 g/dL of monoclonal IgG_3 in the plasma. In vivo whole blood viscosity is not necessarily identical to in vitro serum viscosity (relative to water: normal range 1.4–1.8 centipoise [cp]). Therefore, serum viscosity measurement does not consistently correlate with clinical symptoms among individual patients. Most patients will be symptomatic at levels of 6–7 cp, but some will be symptomatic at levels of 3–4 cp, and others not until levels of 8–10 cp are reached. Early manifestations of hyperviscosity-related retinopathy in Waldenström's macroglobulinemia can be detected in the peripheral retina at a serum viscosity as low as 2.1 cp and IgM levels below 3 g/dL, using indirect ophthalmoscopy. Finally, the tendency of many hospitals to outsource serum viscosity to reference laboratories renders this test potentially less useful than it once was due to uncertainties related to specimen integrity while in transit and to turnaround time.

Current management/treatment

The accepted treatment for hyperviscosity due to underlying lymphoplasmacytic proliferation (Waldenström's or multiple myeloma) is TPE. However, systemic therapy is needed to treat the underlying disorder. Once diagnosed with Waldenström's macroglobulinemia, the patient is placed into a risk category to determine the treatment approach. For those with preserved hematological function and IgM MGUS (<10% lymphoplasmacytic marrow infiltration) watchful waiting is most appropriate. Patients with mild anemia, thrombocytopenia, and/or peripheral neuropathy, and/or hemolytic anemia uncontrolled with corticosteroids should receive single agent rituximab. Patients with constitutional symptoms, hematological compromise, and bulky disease should receive a multiagent cytoreduction protocol with dexamethasone, rituximab and cyclophosphamide. Additionally, patients in the last risk category with symptoms consistent with hyperviscosity should undergo plasma exchange before commencement of cytoreductive therapy. Targeted therapies and transplant approaches have also been used to affect long-term clinical control of the lymphoplasmacytic disease. Pregnant patients unable to receive systemic therapy may be candidates for TPE.

Rationale for therapeutic apheresis

Plasma removal has been successfully employed in the treatment of hyperviscosity syndrome in Waldenström's macroglobulinemia since the 1950's. Early reports demonstrated that manual removal of 8 L over 2 weeks could relieve symptoms of hyperviscosity syndrome. Current automated instrumentation allows removal of 8 L of plasma can be accomplished in two consecutive daily treatments. As the M-protein level rises in the blood, its effect on viscosity increases logarithmically which eventually will push a patient into his/her symptomatic threshold. Likewise, a relatively modest removal of M-protein from the plasma using TPE will have a logarithmic viscosity-lowering effect. Thus plasma exchange is both rapid and efficient in relieving hyperviscosity. Plasma viscosity is a major determinant of capillary blood flow. TPE dramatically increases capillary blood flow, measured by video microscopy, after a single procedure. Rituximab is indicated for patients with certain risk factors (see above), however approximately 50% will experience an increase ("flare") in IgM of $\geq$25% compared to their pretreatment level within 4 weeks of initiation of treatment. Those with IgM $\geq$5000 mg/dL at the time of rituximab initiation are at a higher risk of symptomatic hyperviscosity should the flare occur; prophylactic TPE is recommended for these patients. Careful clinical monitoring, as well as viscosity and IgM levels are recommended during treatment to determine if subsequent TPE procedures are necessary.

Despite the absence of Type I evidence to support the use of TPE or plasmapheresis in the treatment of hyperviscosity syndrome, there have accumulated more than 40 years of reports and case series with consistently positive results.

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 plasma volume expansion. Therefore an empirical exchange of 1–1.5 plasma volumes per procedure seems reasonable. A direct comparison trial demonstrated that centrifugation apheresis is more efficient than cascade filtration in removing M-protein. Cascade filtration and membrane filtration techniques have been described in case reports, but most American institutions employ continuous centrifugation TPE.

Volume treated: 1–1.5 TPV **Frequency:** Daily
Replacement fluid: Albumin

Duration and discontinuation/number of procedures

Patients can be treated daily until acute symptoms abate (generally 1–3 procedures). At that point, serum viscosity measurement can be repeated to determine the point at which the patient experiences symptomatic hyperviscosity relief. Retinal changes in otherwise asymptomatic patients with Waldenström's macroglobulinemia respond dramatically to a single plasma exchange with marked or complete reversal of the abnormal exam findings. An empirical maintenance schedule of one plasma volume exchange every 1–4 weeks based on clinical symptoms or retinal changes may be employed to maintain clinical stability pending a salutary effect of medical therapy (e.g., chemotherapy, targeted therapy, etc.). Prophylactic TPE to lower IgM to <5000 mg/dL may be performed in preparation for a treatment regimen that includes rituximab.

References [666–686]

*As of October 19, 2012 using PubMed and the MeSH search terms hyperviscosity, Waldenström's macroglobulinemia, myeloma and plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

IMMUNE COMPLEX RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Incidence: 0.7/100,000/yr	**Procedure** TPE	**Recommendation** Grade 2B	**Category** III
# of reported patients*: >300			
RCT	**CT**	**CS**	**CR**
7 (196)	0	21 (295)	NA

Case series and RCT have not distinguished between the various causes of RPGN making results difficult to interpret. RCTs have included immune-complex RPGN as well as ANCA-associated RPGN, which is discussed in a separate fact sheet.

Description of the disease

Immune complex glomerulonephritis is one cause of the clinicopathologic entity, RPGN. RPGN consists of loss of kidney function over weeks, with the histologic finding of crescent formation in over 50% of glomeruli. These crescents, a response to renal injury, represent a proliferation of cells within Bowman's space of the glomerulus due to the extravasation of proteins into this space. These cells consist of proliferating parietal epithelial cells as well as infiltrating macrophages and monocytes.

RPGN is NOT A SINGLE DISEASE ENTITY but is a clinical syndrome that can result from a number of etiologies. Systemic complaints, including the renal-pulmonary syndrome, are common. RPGN is divided into three categories based on the immunoflourescence pattern of injury on kidney biopsy. These categories are:

1. Linear deposits of IgG due to autoantibodies to type IV collagen representing anti-GBM GN. It accounts for 15% of cases (see fact sheet on anti-GBM disease).
2. Granular deposits of immune complexes caused by a variety of GNs including post-streptococcal GN, HSP, IgA nephropathy, membranoproliferative GN, cryoglobulinemia, and lupus nephritis. Immune-complex RPGN accounts for 24% of cases of RPGN (see fact sheets on immune-complex RPGN, HSP, and IgA nephropathy).
3. Minimal immune deposits in the glomerulus with the presence of antineutrophil antibodies [either C-ANCA (cytoplasmic) or P-ANCA (perinuclear)] in the serum. This pauci-immune RPGN, also referred to as ANCA-associated RPGN, is seen in granulomatosis with GPA and MPA. GPA and MPA are related systemic vasculitidies, with ANCA positivity and similar outcomes. The majority of patients who present with RPGN are ANCA positive and are therefore in this category. C-ANCA is more often associated with GPA, and P-ANCA with MPA. Antibodies against LAMP-2 are commonly present (see fact sheet on ANCA-associated RPGN).

It is important to identify the specific category of RPGN present in their patient as TPE treatment protocols and responses differ.

Current management/treatment

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

Rationale for therapeutic apheresis

Because of the benefit of TPE in anti-GBM, it was applied to other causes of RPGN. While early trials and series included all categories of RPGN, subsequent trials have excluded anti-GBM. The role of TPE has been examined in seven trials which include both pauci-immune (ANCA-associated RPGN) and immune-complex RPGN. There are no trials of TPE for only immune-complex RPGN. In three out of seven trials that included a mixture of immune-complex RPGN and pauci-immune RPGN, there was no benefit of TPE over standard therapy. Two trials that included immune-complex RPGN and pauci-immune RPGN showed benefit in patients who were dialysis-dependent at the time of presentation, and no benefit to those who had mild disease. In two small trials (14 and 15 patients) with a mixture of immune-complex and pauci-immune RPGN, benefit was seen in all patients. In a review of these trials in the Cochrane Database, the data were interpreted to suggest that TPE may be beneficial for dialysis-dependent patients presenting with severe renal dysfunction; however, there is no therapeutic benefit over immunosuppression alone in milder disease. The predominance of pauci-immune (ANCA-associated) RPGN cases in these trials may account for these beneficial results, making it less clear what effect TPE has on immune complex RPGN. Rarely, TPE may be indicated for pulmonary hemorrhage in non-anti-GBM cases.

Evidence of efficacy of TPE in most causes of immune-complex RPGN is lacking. 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 (see fact sheets on Immunoglobulin A nephropathy and Henoch-Schönlein purpura). Randomized trials of TPE in lupus nephritis have shown no benefit (see fact sheet on SLE). TPE in cryoglobulinemia has proven successful in several series (see fact sheet on cryoglobulinemia).

A single trial of 44 RPGN patients (6 with anti-GBM, 33 with pauci-immune RPGN and 5 with immune-complex RPGN), compared TPE to immunoadsorption using a Staphylococcal protein A agarose column. No difference was found in outcomes between the two treatment groups with both demonstrating improvement.

Technical notes

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

Volume treated: 1–1.5 TPV	**Frequency:** Every other day
Replacement fluid: Albumin	

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 TPE if there is no response after 4 weeks of therapy as outlined above.

References [119, 563, 687–701]

*As of October 21, 2012 using PubMed and the MeSH search terms plasma exchange or plasmapheresis and RPGN or glomerulonephritis or post-streptococcal glomerulonephritis or membranoproliferative glomerulonephritis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

IMMUNE THROMBOCYTOPENIA

Incidence: Adult:38/1,000,000/yr; Child: 46/1,000,000/yr	**Condition**	**Procedure**	**Recommendation**	**Category**
	Refractory	TPE	Grade 2C	IV
	Refractory	IA	Grade 2C	III

# of reported patients*: 100–300

	RCT	**CT**	**CS**	**CR**
TPE	0	0	3 (26)	2 (2)
IA	0	0	5 (132)	0

ITP = Immune thrombocytopenia

Description of the disease

Immune thrombocytopenia (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. Primary ITP, which is a diagnosis of exclusion, is characterized by isolated thrombocytopenia without known initiating or underlying cause. 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, acute ITP resolved in 76% within 6 months, and the remainder had chronic thrombocytopenia, which persisted for >6 months. Remission occurred in 37% of chronic cases. Adult ITP, which predominantly affects women aged 18–40 years old, usually has an insidious onset and 40–50% become chronically thrombocytopenic. Up to 10% of adult ITP is secondary to an underlying primary disorder or stimulus, such as SLE, lymphoproliferative disorders, drug ingestion, primary immunodeficiency or infections, especially hepatitis and HIV. ITP in adults is more serious than in children, because the risk of fatal bleeding increases with age. At platelet counts $<30 \times 10$/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 $>20–30 \times 10^9$/L unless bleeding occurs. First-line therapies are oral corticosteroids (1–2 mg of prednisone/kg/day), IVIG at 1 g/kg/day for 1–2 days, and IV anti-RhD (50–75 μg/kg). In adults, corticosteroids remain the standard primary therapy. In children, IVIG or anti-RhD may be substituted for prednisone for rapid response. If thrombocytopenia persists or recurs, splenectomy is often preferred as second-line therapy but other agents, such as rituximab, thrombopoietin mimetic drugs, danazol, vinca alkaloids, cyclophosphamide, azathioprine and cyclosporine, may be considered based on bleeding, clinical risks and patient-specific considerations. Splenectomy is deferred in children to avoid overwhelming postsplenectomy infection and to allow for spontaneous remission. Recently published evidence-based and international consensus guidelines are available with recommendations for initial and salvage therapy options for ITP.

Rationale for therapeutic apheresis

Anecdotal case reports and small case series of patients with chronic ITP have described a potential benefit for TPE when combined with other salvage therapies, such as prednisone, splenectomy, IVIG, and cytotoxic agents. However, TPE has been shown to be ineffective in other studies. In one report, no improvement was observed among five patients who underwent TPE for refractory ITP after splenectomy. In another, the 6-month response rate and rate of splenectomy were no different among 12 patients who received TPE plus prednisone compared to seven patients treated with prednisone alone. Extracorporeal IA with Staphylococcal protein A silica (discontinued in the US) may be considered in patients with refractory ITP, with life-threatening bleeding or in whom splenectomy is contraindicated. Staphylococcal protein A has a high affinity for the Fc portion of IgG. IgG and IgG-containing circulating immune complexes 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 entirely derive from quantitative reduction of circulating antibodies. Improvement in ITP may result indirectly from in vivo immunomodulation by the release of protein A into the patient, which can induce 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 one of the larger studies, 72 patients were given six IA treatments over 2–3 weeks with 29 (40%) of the patients continued on low dose corticosteroids during IA therapy. Approximately 25% of the patients had a good response (platelet count$>100 \times 10^9$/L) while 21% had a fair response (platelet count 50–100×10^9/L). Over half the patients (54%) had a poor response. Some experts in the field/treatment consensus guidelines consider IA not to be efficacious in primary ITP (*Cines*, *Provan*). Use of this column is contraindicated in patients on angiotensin converting enzyme (ACE) inhibitors (because of risk of anaphylactic reaction), or with 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 offline 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 volume involved with the procedure.

Volume treated: IA: 1000–2000 mL plasma online; 250–500 mL plasma off-line **Frequency:** IA: Once a week or every 2–3 days
Replacement fluid: IA: NA

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 $>50 \times 10^9$/L or no improvement after about six treatments.

References [172, 702–722]

*As of August 1, 2012, using PubMed and the MeSH search terms immune thrombocytopenia, immunoadsorption, Prosorba, and plasma exchange or plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

IMMUNOGLOBIN A NEPHROPATHY

Incidence: 4 /100,000 with 10% developing RPGN	**Condition**	**Procedure**	**Recommendation**	**Category**
	Crescentic	TPE	Grade 2B	III
	Chronic progressive	TPE	Grade 2C	III

# of reported patients*: <100			
RCT	**CT**	**CS**	**CR**
0	1 (9)	7 (64)	6 (8)

RPGN = rapidly progressive glomerulonephritis

Description of the disease

Immunoglobulin A (IgA) nephropathy is the most common form of glomerulonephritis in the developed world, particularly in Asians and Caucasians. Most cases are restricted to the kidneys. It is frequently asymptomatic but there are reports of slow progression to ESRD over 20 to 25 years in up to 50% of patients. Histologically, glomerular deposits of IgA characterize IgA nephropathy. Roughly 10% of patients present as rapidly progressive crescentic glomerulonephritis (see fact sheet on immune-complex RPGN). The classic presentation for the disease is gross hematuria occurring very shortly after an upper respiratory infection (synpharyngitic) or asymptomatic microscopic hematuria with or without proteinuria. Factors associated with disease progression are hypertension, persistent proteinuria over 1000 mg/day, and elevations in serum creatinine. The rapidly progressive form is characterized by acute kidney injury with gross hematuria. While the pathophysiology has not been definitively characterized, current theory focuses on dysregulation of mucosal immune response: (1) mucosal B cells migrate to the bone marrow where they produce IgA1, (2) IgG antibodies are generated toward this IgA1, that would normally not be present in the circulation, (3) IgA1-IgG and IgA1-IgA1 complexes are deposited in the mesangium of the glomerulus, (4) complement and mesangial IgA receptors are activated, (5) mesangial cell damage activates additional pathways, and (6) glomerulosclerosis and interstitial fibrosis develops. Evidence in support of this includes increased levels of serum IgA, the presence of poorly glycosylated IgA in the serum, and mesangial deposits of IgA. An increased level of plasma IgA alone, however, is insufficient to generate mesangial IgA deposits.

Current management/treatment

Therapy consists of nonspecific blood pressure control, control of proteinuria with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, control of hypercholesterolemia using HMG-CoA inhibitors, omega-3 fatty acids, and glucocorticoids with or without other immunosuppressant agents such as cyclophosphamide or azathioprine.

Rationale for therapeutic apheresis

The rationale for TPE in IGA nephropathy is the removal of circulating pathologic IgA molecules and related immune complexes. Early positive experiences of the use of TPE in treating some forms of RPGN resulted in the application of TPE to cases presenting with RPGN (crescentic) form. In addition, early studies demonstrated that TPE could reduce the circulating IgA levels and decrease IgA immune complexes. The majority of published experience has looked solely at the treatment of the RPGN form of the disease and not the chronic progressive disease.

Case reports and series from previous decades have addressed the treatment of the rapidly progressive form characterized by acute kidney injury and the presence of crescents on renal biopsy. The majority of these patients have been treated with concurrent corticosteroids and/or immunosuppressants. These have reported improvement in kidney function and a decrease in serum IgA with TPE. Numerous authors have found that improvement only occurred in the presence of cellular crescents, and not in sclerotic, scarred glomeruli. Two early reports involving 32 patients used only TPE, without other therapy, and saw improvement in kidney function in 31 of these patients. The single controlled trial (*Roccatello*) examined three patients treated with corticosteroids and immunosuppressants and six who also received TPE. Two of the three patients who received only corticosteroids and immunosuppressants became dialysis dependent while the six receiving TPE demonstrated resolution of renal failure during therapy. However, after discontinuation of TPE, disease progressed in all six, with three being dialysis dependent at 3 years following TPE and the remaining having mild to moderate chronic kidney disease. This trial is representative of the experiences reported in the case series and case reports. TPE may improve function during therapy and delay the time to dialysis-dependence but does not halt disease progression.

Three case series have examined TPE in the chronic progressive form and have found improvement in renal function in 12 of 21 patients with slower disease progression during the course of TPE and a longer time to ESRD. All patients were receiving concurrent corticosteroids or immunosuppressant therapy. However, when TPE was discontinued, the rate of disease progression returned to that seen prior to initiation of TPE and all patients eventually progressed to ESRD.

Technical notes

As described above, the greatest benefit appears to occur in those patients with RPGN and in whom renal biopsy demonstrates cellular crescents. Response appears unlikely to occur in chronic disease, if biopsy demonstrates sclerotic glomeruli, or if there is delay in starting TPE following onset of acute kidney failure.

Volume treated: 1–1.5 TPV
Replacement fluid: Albumin
Frequency: 6–9 over 21 days followed by 3–6 over 6 weeks

Duration and discontinuation/number of procedures

A fixed course of therapy has been used to treat patients presenting with RPGN. Creatinine is monitored to determine response. In chronic progressive disease, chronic therapy with weekly TPE for up to 4 months has been reported.

References [723–737]

*As of March 10, 2012 using PubMed and the MeSH search terms plasma exchange or plasmapheresis and glomerulonephritis, IgA for articles published in the English language. References of the identified articles were searched for additional cases and trials. This fact sheet includes abstracts in the summary of published reports and considers them in determining the recommendation grade and category.

INCLUSION BODY MYOSITIS

Incidence: Rare	**Procedure**	**Recommendation**	**Category**
	TPE	Grade 2C	IV
	Leukocytapheresis	Grade 2C	IV

# of reported patients: <100

RCT	**CT**	**CS**	**CR**
0	0	0	1 (1)

Description of the disease

Inclusion body myositis (IBM) is a rare disease with an estimated prevalence rate of 1–71/100,000. It is a progressive degenerative and inflammatory disorder of skeletal muscle. The disease onset is in middle or later life with weakness and atrophy in skeletal muscles such as quadriceps, wrist flexors, and finger flexors. Dysphagia is also a common finding. Muscle biopsy typically reveals endomysial inflammation and invasion of mononuclear cells into non-necrotic fibers. Its cause is unknown, although T-cells, B-cells, dendritic cells, and autoantibodies (anti-IBM-43) have been implicated.

Current management/treatment

There is no effective treatment for IBM; the disease is unresponsive to steroids or immunosuppressants. IVIG may have a transient effect in certain cases. The disease prognosis in general is poor; treatment is mostly symptomatic and supportive.

Rationale for therapeutic apheresis

A single case report described a patient with biopsy confirmed inclusion body myositis who received 22 leukocytapheresis procedures combined with prednisone and azathioprine. After improvement, during the early induction phase with frequent cytaphereses, the clinical response was subsequently lost during a maintenance course with less frequent procedures.

One retrospective case review series reported improved muscle strength in 32 of 35 patients with treatment-resistant idiopathic inflammatory myopathy after weekly TPE was performed for up to 10 weeks together with either cyclophosphamide or chlorambucil. However, the diagnosis of IBM was not specified and the potential role of TPE in these responses could not be determined.

References [738–740]

*As of July 30, 2012 using PubMed and the MeSH search terms Inclusion body myositis and plasmapheresis, plasma exchange, leukocytapheresis, leukapheresis.

INFLAMMATORY BOWEL DISEASE

Incidence: UC: 35–100/100,000; CD: 27–48/100,000	**Condition**	**Procedure**	**Recommendation**	**Category**
	UC	Adsorptive cytapheresis	Grade $1B^{+}/2B^{++}$	III^{+}/II^{++}
	CD	Adsorptive cytapheresis	Grade 1B	III
	CD	ECP	Grade 2C	III

# of reported patients*: >300	**RCT**	**CT**	**CS**	**CR**
UC	9(553)	NR	13(895)	NR
CD	1(23)	NR	Cytapheresis: 4(90); ECP: 2 (59)	2(3)

CD = Crohn's disease; UC = Ulcerative colitis

$^{+}$The standard of care in US includes immunosuppression with TNFα blockade whereas^{++} conventional therapy in Asia consists of steroids and aminosalicylates alone. It is possible that this accounts for positive outcomes for adsorptive cytotherapy found in Asian, but not North American studies.

Description of the disease

Ulcerative colitis (UC) and Crohn's Disease (CD) are chronic inflammatory diseases of the GI 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 worldwide distribution. Environmental, gut microbiota and genetic factors may lead to leukocyte recruitment to the gut mucosa. The cells, and accompanying cytokines and proinflammatory mediators, cause tissue damage and lead to the clinical manifestations of IBD. 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.

Current management/treatment

First line therapies for IBD include anti-inflammatory, steroid and immunosuppressive medications. Both corticosteroids and 5-aminosalicylic acids (5-ASAs) are effective in achieving remission. In addition, 5-ASAs and immunosuppressant drugs reduce the risk of subsequent relapse of activity in quiescent disease. Complications from chronic steroid administration include steroid resistance, dependency and the sequelae of long-term steroid use. For those with refractory disease thiopurines, immunosuppressive drugs such as azathioprine and 6-mercaptopurine are used. In CD specifically, infliximab, may induce remission and has been FDA cleared for this purpose. Surgical intervention may be necessary in some patients. Selective apheresis is a potentially useful adjunct for the management of IBD with the goal of removing the activated leukocytes or moderating their proinflamatory nature towards an immune modulatory phenotype.

Rationale for therapeutic apheresis

Because of evidence suggesting that granulocytes and proinflammatory monocytes, dysregulated dendritic cell function and subsequent T-cell inflammatory responses agents underly IBD, apheresis therapies targeting these cells have been developed. Apheresis may be useful for those patients who are steroid dependent or have failed other modalities. Numerous observational and retrospective clinical studies without adequate controls show disease response and some have found patients are able to receive lower steroid dose using adsorptive cytapheresis. Several studies show alterations in serum markers of disease activity such as cytokines (TNFα, IL-6, IL-8, and IL-1B) and inflammatory cells in treated patients. A study of granulocytapheresis using Adacolumn found a significant reduction of peripheral blood proinflammatory dendritic cells in samples from UC patients after the procedure. A nonsignificant reduction of serum levels and a rise in IL-10 levels was also detected. In CD patients, a study of the regulatory T-cell profiles between the inflow and outflow of the adsorptive column found elevations of the Treg-related cytokines IL-10 and TGF-β1(anti-inflammatory) in the column outflow. These preliminary data suggest that the procedure may mitigate the pathophysiology of the IBD process. Two uncontrolled case series have been published suggesting that ECP can promote remission for a proportion of patients in the category of steroid and/or immunosuppressant intolerant CD. Further study is warranted to determine if ECP is a viable treatment option for CD.

There are several randomized controlled trials using adsorptive cytapheresis, mostly in UC patients. A small RCT by Sawada et al. employed the Cellsorba system compared to a sham procedure in 19 patients with active moderate to severe active UC. There was an 80% improvement in clinical activity scores (excellent to moderate) in the apheresis group compared to the sham group, 33.3% ($P < 0.05$). A large placebo-controlled trial by Sands et al. which also used a sham apheresis procedure was performed predominantly in North America (215 patients were from US, Canada, Europe and Japan with active moderate to serve UC). The study demonstrated an 18% rate of remission in the apheresis treated group and 13% in the control ($P = 0.430$) and 47% apheresis treated compared with 40% of controls showed some response ($P = 0.386$), suggesting no clinical efficacy of the treatment. A study by Dimness et al. randomized 162 UC patients to 5 or 10 granulocyte-monocyte apheresis procedures using Adacolumn and found no difference in the clinical activity score, remission and response between the two treatment regimens. An RCT of asymptomatic UC and CD patients with low requirements for medical therapy (steroids or aminosalicylates) by Maiden et al. found 24% vs. 16% remission in CD and 48% vs. 16% in UC using the clinical activity index improvement score, suggesting prophylactic treatment may be protective from relapse. Adverse reactions have been infrequently reported and include headache, fatigue, nausea, arm pain, hematoma, and light-headedness.

Technical notes

Two types of selective apheresis devices are the Cellsorba (Asahi Medical, Tokyo, Japan) which is a column containing cylindrical nonwoven 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 min. Some platelets and lymphocytes are also removed by this column. For Adacolumn, venous whole blood is processed at 30 mL/min for 60 min. The Adacolumn is relatively selective for removing activated granulocytes and monocytes. Patients taking ACE inhibitors may experience low blood pressure if undergoing treatment with Adacolumn. Cellsorba and Adacolumn are currently available in Europe and Japan. The two columns have been compared in a prospective clinical trial that demonstrated equivalent response in patients with moderate-to-severe active UC.

Volume treated: Adacolumn: 1,800 mL; Cellsorba: 3,000 mL	**Frequency:** Once per week, more intensive therapy may include daily – two times per week
Replacement fluid: NA	

Duration and discontinuation/number of procedures

The typical length of treatment is 5–10 weeks for Adacolumn and 5 weeks for Cellsorba.

References [741–772]

*As of November 19, 2012 using PubMed and the MeSH search terms inflammatory bowel disease, Crohn's disease, ulcerative colitis or IBD and selective apheresis, leukocytapheresis, LCAP, or GMA for articles published in the English language. References of the identified articles were searched for additional cases and trials.

LAMBERT-EATON MYASTHENIC SYNDROME

Incidence: 7.5/100,000	**Procedure** TPE	**Recommendation** Grade 2C	Category II
# of reported patients*: <100			
RCT	**CT**	**CS**	**CR**
0	0	6 (37)	4 (5)

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 features of the disease are 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 respiratory failure or prolonged apnea after anesthesia. Approximately 60% of patients have small cell lung cancer that may not become radiographically 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 autoantibodies directed at the voltage-gated calcium channel (VGCC) of the nerve terminal. The 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. The antibody to VGCC is found in >75% of LEMS cases associated with primary lung cancer, in approximately 25% of LEMS cases associated with other cancers, and in 50% of LEMS cases without cancer. The antibody is also found in up to 10% of lung cancer patients without LEMS. Antibody levels do not correlate with severity, but may decrease as the disease improves in response to immunosuppressive therapy.

Current management/treatment

Apart from a search for, and treatment of, underlying malignancy, management of LEMS is directed toward support immunosuppression to control production of the offending antibodies and support of acetylcholine-mediated neurotransmission to improve neurological function. Amifampridine or 3,4-diaminopyridine (DAP) has emerged as an effective agent and first choice for symptomatic control in LEMS. It blocks fast voltage-gated potassium channels, prolonging presynaptic depolarization and thus the action potential, resulting in increased release of acetylcholine and also resulting in increased calcium entry into presynaptic neurons. It is generally well tolerated, although rare cardiac toxicity has been reported. 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, such as guanidine hydrochloride, that act to enhance release of acetylcholine from the presynaptic nerve terminal. Guanidine hydrochloride is taken orally in divided doses up to 1,000 mg/day in combination with pyridostigmine. This combination can be used if amifampridine is not available.

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 immunosuppressive medications cyclosporine and cyclophosphamide have also been used. IVIG has been shown effective in LEMS in a randomized, double-blind, placebo-controlled crossover trial involving nine patients. IVIG may be useful in repeated monthly infusion of 2 g/kg given over 2–5 days over upward of 2 years. In addition, rituximab has also shown to be effective in some cases.

Rationale for therapeutic apheresis

The identification of LEMS as an autoantibody-mediated syndrome has led to several attempts to use TPE in its treatment. While no controlled trials exist on the use of TPE in the LEMS, case series has suggested a benefit. In one series, 8 out 9 patients had (*Newsom-Davis*) increase in electromyographic muscle action potential ($P < 0.01$) while receiving TPE and immunosuppression. 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, or who cannot tolerate treatment with IVIG.

Technical notes

The reported TPE regimens vary from 5–15 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 volumes. Of note: improvement may not be seen for the 2 weeks or more after initiation of plasma exchange therapy. This may be due to the slower turnover of the presynaptic voltage gated calcium channel compared to the postsynaptic acetylcholine receptor.

Volume treated: 1–1.5 TPV	**Frequency:** Daily or every other day
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

Treatment should continue until a clear clinical and EMG response is obtained or at least until a 2–3-week course of TPE has been completed. Repeated courses may be applied in case of neurological relapse, but the effect can be expected to last only 2–4 weeks in the absence of immunosuppressive drug therapy.

References [773–787]

*As of July 30, 2012, using PubMed and MeSH search terms Lambert-Eaton Myasthenic Syndrome and plasma exchange, plasmapheresis for journals published in the English language. References of the identified articles were searched for additional cases and trials.

LIPOPROTEIN (A) HYPERLIPOPROTEINEMIA

Incidence: Unknown	**Procedure** LDL apheresis	**Recommendation** Grade 1B	**Category** II
# of reported patients*: 100–300			
RCT	**CT**	**CS**	**CR**
2 (41)	2 (123)	4 (23)	2 (2)

Description of the disease

Lipoprotein (a) (Lp(a)) is a plasma lipoprotein that consists of an LDL particle with an apolipoprotein B and an apolipoprotein (a) bound by a disulfide bond. The normal level of Lp(a) is less than 30 mg/dL (1.6 mmol/L) but levels can vary up to 1000 fold between individuals. Lp(a) levels are genetically controlled. The Lp(a) molecule contains a *kringle* IV type 2 size polymorphism with the number of these repeats being inversely correlated with the Lp(a) level. Lp(a) levels are stable throughout life with little dietary influence.

Lp(a) has structural homology with plasminogen and plasmin. It is a competitive inhibitor of plasminogen activator, inhibiting fibrinolysis. It also inhibits tissue factor pathway inhibitor. The result is enhanced coagulation and inhibition of fibrinolysis producing a prothrombotic state. Lp(a) also deposits LDL cholesterol, recruits inflammatory cells, and promotes binding of pro-inflammatory oxidized phospholipids into the intima of the artery promoting atherosclerosis. The combination of thrombotic potential and accelerated atherosclerosis results in vascular disease with elevations in Lp(a) having been found to be an independent risk factor for coronary artery disease and ischemic stroke. There is no threshold for the cardiovascular effects of Lp(a).

Current management/treatment

Lp(a) is not influenced by diet and this does not play a role in therapy though it does in the reduction of concurrent risk factors such as elevated LDL cholesterol. High dose niacin (1–3 g/day) can lower Lp(a) by 30–40% and reduce cardiovascular risk due to elevated Lp(a) by up to 25%. Additional medications which have been found to reduce Lp(a) include HMGCoA-reductase inhibitors, aspirin, L-carnitine, ascorbic acid, neomycin, calcium channel antagonists, angiotensin converting enzyme inhibitors, androgens, estrogens, and fish oil. These medications result in limited reduction of Lp(a) (less than 10%) with negligible benefit to the patients with extreme elevations.

Rationale for therapeutic apheresis

All currently available LDL apheresis systems have been found to decrease Lp(a) by 40–88%. Case series of the use of LDL apheresis to treat isolated Lp(a) elevations in patients with cardiovascular disease have reported resolution of angina after 3–5 months of treatment, statistically significant reductions in cardiac events and cardiac interventions after implementation of therapy compared to before treatment, and angiographic regression of atherosclerotic plaque with treatment. A controlled trial (*Jaeger*) examined 120 patients with elevations in Lp(a) at or above the 95th percentile of normal who did not have familial hypercholesterolemia. All patients were on maximum lipid lowering therapy with LDL apheresis added when this was no longer tolerated or disease progressed. Lp(a) levels and the annual occurrence of major adverse cardiac events were compared for the time period prior to the start of LDL apheresis (5.6 ± 5.8 years) and after initiation of apheresis (5.0 ± 3.6 years). This study found a significantly lower Lp(a) (4.00 mmol/L versus 1.07 mmol/L, $P < 0.0001$) and significantly fewer cardiac events per patient per year (1.056 vs. 0.144, $P < 0.0001$) after initiation of treatment. A randomized controlled trial of 21 patients (*Stefanutti*) with isolated Lp(a) and angiographically documented coronary artery disease compared LDL apheresis and standard medical care ($n = 10$) to standard medical care ($n = 11$). Lp(a) increased by $14.7 \pm 36.5\%$ in the standard medical care group at 12 months but decreased by $57.8 \pm 9.5\%$ in the group treated with LDL apheresis. There were no differences in new cardiac events and interventions at 12 months between the two groups. The authors hypothesized that the relatively short follow-up of 12 months may not have been sufficient to demonstrate an effect. A second randomized trial (*Bohl*) examined the acute effects of LDL apheresis in 20 patients with coronary artery disease and Lp(a) >60 mg/dL (15 treated and 5 control). Lp(a) was reduced by 55% with a single treatment. At 24 h, ejection fraction and myocardial perfusion each demonstrated a small but statistically significant improvement that returned to baseline at 96 h.

Technical notes

The six available LDL apheresis devices (see fact sheet on familial hypercholesterolemia) are all capable of removing Lp(a) with similar degrees of reduction. There have been no reports of the use of TPE to treat elevations of Lp(a).

ACE inhibitors are contraindicated in patients undergoing adsorption-based LDL apheresis. The columns function as a surface for plasma kallikrein generation, which, in turn, converts bradykininogen to bradykinin. Kininase II inactivation of bradykinin is prevented by ACE inhibition resulting in unopposed bradykinin effect, hypotension and flushing. This is not seen with the HELP system.

Some LDL apheresis systems have also been found to result in significant removal of vitamin B12, transferrin, and ferritin. This may be the cause of the anemia seen in patients undergoing therapy and supplementation may be necessary.

The European Atherosclerosis Society Consensus Panel recommends the reduction of Lp(a) to less than the 80th percentile of normal, <50 mg/dL (2.77 mmol/L). The HEART-UK criteria for the use of LDL apheresis includes patients with progressive coronary artery disease, hypercholesterolemia, and Lp(a) >60 mg/dL (>3.3 mmol/L) in whom LDL cholesterol remains elevated despite drug therapy. Other LDL apheresis treatment criteria, such as those published by the FDA, International Panel on Management of Familial Hypercholesterolemia, and the German Federal Committee of Physicians and Health Insurance Funds do not include Lp(a) in their criteria for LDL apheresis. However, in Germany LDL apheresis is used in Lp(a) hyperlipoproteinemia in the presence of progressive coronary artery disease and failure of drug therapy.

Volume treated: Varies according to device **Frequency:** Once every 1–2 weeks
Replacement fluid: NA

Duration and discontinuation/number of procedures

Treatment is continued indefinitely, adjusted to maintain the Lp(a) below 50 mg/dL (2.77 mmol/L).

References [788–801]

*As of October 21, 2012 using PubMed and the MeSH search terms lipoprotein (a) and apheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

LIVER TRANSPLANTATION, ABO INCOMPATIBLE

Incidence:	Condition	Procedure	Recommendation	Category
LDLT: Rare; DDLT: Infrequent	Desensitization (LDLT)	TPE	Grade 1C	I
	Desensitization (DDLT)	TPE	Grade 2C	III
	Humoral rejection	TPE	Grade 2C	III

# of reported patients*: >300

	RCT	CT	CS	CR
LDLT	0	0	3 (332)	1 (1)
DDLT	0	0	6 (54)	9 (9)

LDLT = live donor liver transplant; DDLT = deceased donor liver transplant.

Description of the disease

Due to a relative shortage of compatible organs for transplantation, ABO incompatible (ABOi) transplants are being increasingly used. As of Feb 2013, more than 15,000 candidates were on the United Network for Organ Sharing (UNOS) waitlist to receive a liver allograft. In 2012, 4% of patients on the UNOS liver waitlist received an allograft from live donors. Major incompatibility refers to the presence of natural antibodies in the recipient against the donor's A or/and B blood group antigen. These antibodies may cause hyperacute/acute humoral rejection of the organ due to endothelial damage (A and B antigens are expressed on vascular endothelium). Major ABO incompatibility exists in approximately 35% of random donor–recipient pairs. Minor incompatibility occurs where the organ donor has naturally occurring ABO antibodies against the recipient. Donor lymphocytes present within the graft (known as passenger lymphocytes) may produce antibodies against recipient RBCs. Biochemical PLS, indicated by elevation of laboratory parameters of hemolysis is relative common in liver transplantation, however only a small number of such patients develop clinical signs and symptoms of hemolysis.

Current management/treatment

There has been significant progress in the use of TPE perioperatively in major ABOi DDLT and for preconditioning/AMR treatment in major ABOi LDLT. In the DDLT setting, TPE is typically instituted immediately before and sometimes both before and after transplantation in an attempt to prevent hyperacute rejection and acute AMR. ABOi LDLT has been increasingly used in Japan with patients being treated with rituximab, TPE and hepatic infusion with prostaglandin E1 and methylprednisolone. Recent data suggest a high 2 yr graft survival of 80%. Intestinal perforation is one of the major risks associated with local intravascular infusion of these medications. Similar to the ABOi renal transplant setting, rituximab appears to be as effective as splenectomy in enabling ABOi LDLT. Recent studies have not utilized splenectomy, and some groups use immunoadsorption columns in place of TPE. The A_2 blood group has reduced expression of the A antigen on endothelium (and RBCs). Unlike A_2/A_2B into B deceased donor renal transplantation that has been shown to be successful for more than a decade, A_2 into non-A DDLT has not been frequently attempted. However, a recent large retrospective series on DDLT suggests that A_2 into O transplants may be safe with similar graft and overall survival relative to ABO-compatible DDLT. A small number of studies also suggest that TPE, in combination with enhanced immunosuppression may be effective in reversing humoral rejection in the liver allograft. In minor ABOi liver transplantation, rare cases of severe hemolysis due to PLS are typically treated with packed RBC transfusions. Infrequently, in patients with severe refractory hemolysis, TPE or erythrocytapheresis (with allograft donor type red cells or O RBCs) has been utilized.

Rationale for therapeutic apheresis

There are no controlled clinical trials using TPE in ABOi liver transplantation. Given that both hyperacute rejection, and acute AMR are definitive risks in ABOi liver transplants, TPE has been used as the key therapeutic modality to reduce anti-A or anti-B antibody titers in the peri-transplant period with the goal of preventing rejection and facilitating graft survival. In ABOi LDLT transplantation, TPE is extensively used as part of a preconditioning protocol to lower antibody titer below a critical threshold (which differs based on titration method/technique) prior to the transplant procedure. In DDLT, TPE procedures are often utilized in the urgent/emergent setting after a deceased ABOi allograft has been identified, making a thorough analysis of TPE efficacy challenging. Similarly, TPE has also been used in the setting of AMR in the liver allograft to decease levels of ABO antibodies.

Technical notes

The replacement fluid for TPE is plasma, or albumin and plasma (plasma should be compatible with both the recipient and donor). Plasma use may need to be more aggressive in the setting of ABOi liver transplantation due to coagulopathy secondary to liver failure in the recipient.

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

Duration and discontinuation/number of procedures

The goal should be to reduce the antibody titer to less than a critical threshold prior to taking the patient to transplant. It is important to note that this critical titer will need to be determined by each program embarking on this type of transplant, given that titer results can vary widely depending on titration method and technique. The number of TPE procedures required depends upon the patient's baseline ABO titer, and on the rate of antibody production/rebound. Unlike in ABOi renal transplantation, the predictive value of post-transplant titers is less well established. Patients should be monitored closely for graft function before discontinuation of TPE.

References [802–824]

*As of October 16, 2012 using PubMed and the MeSH search terms search terms ABO incompatible, liver transplantation, plasma exchange, plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

LUNG ALLOGRAFT REJECTION

Incidence: Lung Transplants: ~1800 in US (2011); BOS: 25% at 2.5 years and 50% at 5.6 years post-transplant;AMR: Unknown	**Condition**	**Procedure**	**Recommendation**	**Category**
	BOS	ECP	Grade 1C	II
	AMR	TPE	Grade 2C	III

# of reported patients*: 100–300

	RCT	**CT**	**CS**	**CR**
ECP	0	0	8 (218)	5 (5)
TPE	0	0	3 (30)	2 (2)

AMR = antibody mediated rejection; BOS = Bronchiolitis Obliterans Syndrome

Description of the disease

Data from the International society for Heart and Lung Transplantation (ISHLT) registry, representing more than 10,000 transplants followed from April 1994 through June 2006, indicates that a significant percentage of patients go on to develop Bronchiolitis Obliterans Syndrome (BOS) with 25% developing this condition in 2.5 years and 50% in 5.6 years after transplant. Acute rejection is one of the major risk factors for chronic rejection which remains the most common cause of death after the first post-transplant year. Chronic rejection is manifested as BOS. BOS is a pathological process that affects small airways and is a significant cause of allograft chronic dysfunction. BOS can be difficult to diagnose by transbronchial biopsy and thus the diagnosis is made on the basis of graft deterioration due to persistent airflow obstruction instead of histologic confirmation. The diagnosis of BOS is defined by a sustained (greater than 3 weeks) decline in expiratory flow rates, provided that alternative causes of pulmonary dysfunction have been excluded. According to the ISHLT system used widely to define the severity of BOS, Stage 0 refers to no significant abnormality and FEV_1 (Forced expiratory volume in 1 s) >90% of best postoperative value and FEF (Forced midexpiratory flow) >75% of baseline, Potential BOS (0-p) is defined as 81–90% of FEV_1 and/or FEF ≤75% of baseline, BOS Stage 1- 66%–80% of FEV_1, Stage 2- 51%–65% of FEV_1, while Stage 3 refers to severe BOS with FEV_1 <50%. The most precipitous decline in airflow typically occurs in the first six months following a diagnosis of BOS, although time of onset of BOS and rate of decline of FEV_1 are highly variable. Single lung transplantation conveys a higher risk for earlier onset of BOS compared to bilateral transplantation, and an unfavorable outcome appears to be associated with rapid onset of BOS, female gender, and pretransplant idiopathic pulmonary fibrosis. Recent case reports and series suggest that AMR should be considered a potential cause of graft dysfunction, particularly when resistance to corticosteroid therapy is encountered. Formal criteria for the diagnosis of pulmonary AMR have now been put forth by ISHLT.

Current management/treatment

At the time of transplantation, many transplant centers now employ an induction regimen that includes infusion of an antibody that targets activated host lymphocytes. Such agents include polyclonal anti-T-cell preparations like antithymocyte globulin (ATG), or monoclonal agents aimed at lymphocyte surface molecules such as CD3 (OKT3), IL-2 receptor/CD25 (daclizumab, basiliximab) or CD52 (Campath-1H). Maintenance immunosuppressive therapy after lung transplantation typically consists of a three-drug regimen that includes a calcineurin inhibitor (cyclosporine or tacrolimus), an antimetabolite (azathioprine or mycophenolate mofetil), and steroids. Short courses of intravenously pulsed corticosteroids, followed by a temporary increase in maintenance doses for a few weeks, are the preferred treatment for uncomplicated acute rejection. The initial treatment of BOS usually consists of repeated pulses of high-dose methylprednisolone. Additional therapeutic options are augmentation of existing regimens and/or switching within classes of drugs. Successful treatment of BOS is usually defined as ''stabilization'' or ''slowing'' of FEV_1 decline instead of true improvement or normalization of airflow. For patients with unresponsive BOS, salvage immunosuppressive regimens have included methotrexate, ATG, or OKT3. Recently, the macrolide antibiotic azithromycin has shown efficacy in improving FEV_1 in lung transplant recipients suffering from BOS. Some reports suggest that post-transplant pulmonary capillaritis that is seen in some lung rejection patients is a form of acute allograft rejection that is clinically and histologically distinct from BOS, less responsive to corticosteroid therapy, and possibly responsive to TPE.

Rationale for therapeutic apheresis

The first report of ECP in a lung transplant patient was published in 1995. At first, ECP was used in the context of refractory BOS (Stages 2–3) in which benefit was demonstrated by initial stabilization or improvement in FEV_1. Since then, some groups have utilized ECP as an effective therapeutic modality for stabilization of lung function in patients with persistent acute rejection and early BOS (Stages 0-p-1), thus preventing further loss of pulmonary function. As ECP is not likely to reverse fibroblast proliferation in the transplanted lung, earlier initiation of ECP for BOS post-transplant may arrest BOS progression. Three recent large studies (60, 51, and 24 patients) suggest that ECP significantly reduces the rate of decline in lung function in transplant recipients with BOS as measured by FEV_1. The potential mechanism of action of ECP is discussed in the fact sheet on Cardiac Transplantation, ABO compatible. ECP is generally well tolerated and does not appear to predispose to increased risk of infection. Both anti-HLA and antiendothelial antibodies have been proposed in mediating AMR. Recent reports suggest that TPE (in combination with IVIG, and anti- B cell/plasma cell therapies) may be efficacious in treating AMR.

Technical notes

In the largest case series of ECP in BOS, 24 ECP treatments were administered during a 6-month period, delivered as 2 treatments on successive days. 10 treatments were performed over the first month, followed biweekly for the next 2 months (8 treatments), and then monthly for the remaining 3 months (6 treatments).

Volume treated: ECP: MNC product of 200–270 mL. The 2-process method collects and treats MNCs obtained from processing 2 TBV; TPE 1–1.5 TPV

Frequency: ECP: See above; TPE: Daily or every other day

Replacement fluid: ECP: NA; TPE: Albumin, plasma

Duration and discontinuation/number of procedures

The optimal duration of treatment is not well established. If clinical stabilization occurs with ECP, long-term continuation may be warranted to maintain the clinical response. In a recent 10 year single center experience, 24 treatments were the initial ''dose'' and long term continuation (two treatments per month) was recommended for responders. For pulmonary AMR, TPE treatment may be discontinued with reversal of rejection as evidenced by an improvement in allograft function/ reduction in donor specific antibody levels.

References [825–849]

*As of December 26, 2012 using PubMed and the MeSH search terms pulmonary/lung transplantation, pulmonary/lung rejection, bronchiolitis obliterans syndrome, BOS, extracorporeal photopheresis, photopheresis, plasma exchange and plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

MALARIA

Incidence: In 2010, 216 million cases worldwide; 1688 imported cases; (176 severe; 9 deaths) in US	**Condition** Severe	**Procedure** RBC exchange	**Recommendation** Grade 2B	**Category** II

# of reported patients*: <100 RBC exchange; >300 Manual exchange transfusion

	RCT	**CT**	**CS**	**CR**
RBC exchange	0	0	8 (34)	13 (17)
Manual exchange transfusion	0	8 (279)	8 (101)	13 (13)

Description of the disease

Malaria is a vector-borne protozoal infection caused by *Plasmodium vivax, P. ovale, P. malariae* or *P. falciparum*. Global mortality rates have decreased since 2000, but an estimated 655,000 deaths were still attributed to malaria in 2010. The highest mortality occurs with *falciparum* malaria in African regions and among pregnant women, nonimmune travelers, those with HIV/AIDS and children under 5 years of age. The intraerythrocytic stage of the *Plasmodia* life cycle is responsible for many of the pathological disease manifestations. Infected red cells provide the vehicle for transmission by mosquitoes or blood transfusion. Infectious symptoms usually begin within 10 days to 4 weeks after inoculation. Parasitemia leads to red cell rigidity and aggregation, microvascular obstruction, hemolysis and activation of inflammatory cells and cytokines. These lead to fever, malaise, chills, headache, myalgia, nausea, vomiting and, in some cases, anemia, jaundice, hepatosplenomegaly and thrombocytopenia. Because of its invasiveness and drug resistance, *P. falciparum* is responsible for most of the severe malaria cases, which are characterized by high-grade (> 5%) parasitemia with or without single organ or multisystem dysfunction. Organ manifestations of severe malaria include impaired consciousness, coma, seizures, pulmonary edema, acute respiratory distress syndrome, shock, DIC, spontaneous bleeding, renal failure/hemoglobinuria, clinical jaundice, severe anemia (Hgb <5 g/dL), acidosis, and hypoglycemia. The mortality rate with severe *falciparum* malaria ranges from 5–20%. Poor prognostic features vary based on patient populations, but have included acidosis, impaired consciousness, preexisting chronic disease, progressive end-organ dysfunction, anemia, and hyperparasitemia >10%. Because severe complications can develop in up to 10% of nonimmune travelers with *P. falciparum*, symptomatic patients with a positive travel history should be promptly evaluated and treated. Diagnosis typically involves identification and quantitation of intraerythrocytic organisms on thick or thin blood smears. A rapid diagnostic immunoassay is now available in the U.S. for confirmation, and such assays are increasingly being used in developing countries.

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. Management of imported, uncomplicated malaria in the U.S. is outlined in guideline documents available from the Centers for Disease Control and Prevention (CDC). Single or combination oral agent regimens include chloroquine, hydroxychloroquine, or quinine (alone or with doxycycline, tetracycline or clindamycin), atovaquone-proguanil, artemether-lumefantrine, mefloquine, and primaquine. Artemisinin-based combination therapy is recommended for *falciparum* malaria in endemic countries. Severe malaria should be treated promptly with intravenous quinidine gluconate (a stereoisomer of quinine) with transition to oral quinine-combinations when stable. Intravenous artesunate is available through the CDC for intolerance or contraindications to quinidine or for drug-resistance manifested by parasitemia >10% at 48 h. of treatment. *Falciparum* malaria with more severe anemia, hypoxemia, hyperparasitemia, neurologic manifestations (i.e., cerebral malaria) or metabolic derangements, particularly in children, asplenic or immunocompromised individuals, requires aggressive parenteral antimalarials. Intensive care support is also often necessary to manage volume resuscitation, electrolyte replacement, antiseizure medications, transfusions as indicated, airway control and/or ventilatory maintenance.

Rationale for therapeutic apheresis

RBC exchange or manual exchange transfusion (with whole blood or red cell replacement) in severely ill patients with hyperparasitemia (i.e., >10%) appears to improve blood rheological properties, capillary perfusion and microcirculatory flow. Whole blood exchange may also, theoretically, reduce pathogenic humoral mediators such as parasite and host toxins, hemolytic metabolites and cytokines. A number of reports have described rapid clinical improvement and improved parasite clearance times with severe *P. falciparum* malaria when RBC exchange or manual exchange transfusion is used in conjunction with intravenous quinidine therapy. By comparison, parasite clearance time with artesunate alone is rapid and equivalent to that achieved with automated RBC exchange. The role for and potential benefit of automated or manual red cell exchange in severe malaria is controversial and based on observational retrospective clinical data. A meta-analysis of 279 patients from 8 case-controlled trials found no survival benefit of manual exchange transfusion compared to antimalarials and aggressive supportive care alone. Notably, there were major differences in the exchange transfusion methodologies, the severity of illness in the transfusion versus nontransfusion groups and other confounding variables that call into question the accuracy of these comparisons and the analyses. Despite these limitations and lack of prospective, randomized controlled trials, the CDC recommends exchange transfusion be strongly considered for persons with a parasite density >10% or if complications such as cerebral malaria, acute respiratory distress syndrome, or renal complications exist. The recommended goal is a parasite density below 1%. Quinidine administration should not be delayed and can be given concurrently; limited studies suggest that RBC exchange does not significantly affect drug levels. The UK treatment guidelines of severe malaria also suggest consideration of RBC exchange for severely ill patients with >10% parasitemia. The WHO guidelines make no recommendation regarding the use of exchange transfusion, citing the lack of consensus on indications, benefits, dangers and practical technical details. Rare case reports have described using adjunctive plasmapheresis with automated RBC exchange; however, lack of published experience precludes assessment of this procedure in patients with severe malaria.

Technical notes

Automated apheresis instruments calculate the amount of RBCs required to achieve the desired post-procedure hematocrit, fraction of red cells remaining and, by inference, the estimated final parasite load. A single two-volume RBC exchange can reduce the fraction of remaining patient red cells to roughly 10–15% of the original. The risks include circulatory overload, transfusion reactions, blood-borne infection (especially in developing countries), hypocalcemia, RBC allosensitization and possible need for central venous access.

Volume treated: 1–2 total RBC volumes **Frequency:** Usually one to two treatments
Replacement fluid: RBCs (consider leukoreduced), plasma

Duration and discontinuation/number of procedure

Treatment is discontinued after achieving significant clinical improvement and/or <1% residual parasitemia.

References [627, 850–889]

*As of July 3, 2012 using PubMed and the MeSH search terms malaria, falciparum, apheresis, RBC exchange, 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.

MULTIPLE SCLEROSIS

Incidence: 5–30/100,000/yr (US)	**Condition**	**Procedure**	**Recommendation**	**Category**
	Acute CNS inflammatory demyelinating	TPE	Grade 1B	II
	disease unresponsive to steroids	IA	Grade 2C	III
	Chronic progressive	TPE	Grade 2B	III

# of reported patients*: >300				
	RCT	**CT**	**CS**	**CR**
Acute CNS inflammatory demyelinating disease	3 (306)	1 (41)	7 (86)	5 (5)
Chronic progressive	7 (285)	0	10 (165)	3 (4)

Description of the disease

Multiple sclerosis (MS) is a relapsing and often progressive disorder of central nervous system (CNS) white matter demyelination. It presents in early adulthood and has variable prognosis. Eighty percent of MS is the relapsing-remitting MS (RRMS) form where signs and symptoms evolve over days, stabilize and then improve within weeks. Corticosteroids speed recovery, but the response decreases over time. Persistent symptoms may develop and the disease may progress between relapses, referred to as secondary progressive MS. 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 of the cerebrum, brain stem, cerebellum, and spinal cord. A more severe clinical course can be predicted by frequent relapses in the first 2 years, primary progressive form, male sex, and early permanent symptoms. Acute CNS inflammatory demyelinating disease is usually secondary to MS but includes cases of acute transverse myelitis and neuromyelitis optica (NMO or Devic'syndrome; see fact sheet on NMO).

Current management/treatment

Genetic and environmental factors 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 of the immune system. Standard treatment for MS exacerbation is intravenous administration of high dose methylprednisolone. If unresponsive, a second steroid pulse is given after an interval of 10–14 days. In acute, severe attacks of MS in patients who fail initial treatment with high-dose steroids, TPE may be beneficial. Disease modifying treatment in RRMS includes: interferon beta-1a and glatiramer acetate as first line treatment as well as many others such as azathioprine, mitoxantrone hydrochloride, cyclophosphamide, intravenous immunoglobulin, rituximab, natalizumab, fingolimod, and dalfampridine depending on the disease severity and treatment response. TPE has not been specifically studied in RRMS.

An adequate treatment for primary progressive MS does not exist. Multiple randomized controlled trials demonstrate small to no benefit of TPE in conjunction with other immunosuppressive drugs in patients with chronic progressive MS. It is not clear whether the cost and potential adverse effects of TPE outweigh the potential small benefit.

Autologous HSC transplantation has also been used to successfully treat both relapsing and remitting MS as well as primary progressive MS refractory immunosuppressive therapy in an attempt to "reboot" the immune system.

Rationale for therapeutic apheresis

MS is an autoimmune disease with an unclear pathogenesis. Complement-dependent demyelinating IgG is seen in approximately 30% of patients and recently an antibody to potassium channel KIR4.1 has been identified in 47% of MS patients. Rituximab has been reported to reduce gadolinium (Gd)-enhancing MRI lesions and relapses in RRMS. TPE may benefit MS patients by removing the autoantibody, such as antimyelin antibody, or modulating immune response. There have been four immunopathological patterns of demyelination in early MS lesions. The characteristics of demyelination for each pattern are: type I – T-cell/macrophage-associated, type II – antibody/complement-associated, type III – distal oligodendrogliopathy, and type IV – oligodendrocyte degeneration. A study of patients with fulminant CNS inflammatory demyelinating disease demonstrated that all 10 patients with type II but none of the 3 with type I or 6 with type III had substantial improvement with TPE (*Keegan*).

In addition to TPE, IA has also been used to treat RRMS. A case series of 12 patients treated with IA found improvement in EDSS. (*Moldenhauer*) A second case series of 10 patients with CNS demyelination due to acute MS unresponsive to steroids reported a clinical response in 66% of patients treated with IA (*Trebst*).

TPE has also been reported to be used for MS patients who were treated with natalizumab and developed progressive multifocal leukoencephalopathy for the purpose of removal of natalizumab (low volume distribution) (see fact sheet on overdose, envenomation, and poisoning).

Technical notes

Volume treated: 1–1.5 TPV	**Frequency:** Acute: 5–7 over 14 days; Chronic progressive: weekly
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

In acute MS relapse unresponsive to steroids, 5–7 TPE procedures have a response rate of approximately 50%. Studies have found that early initiation of therapy, within 14–20 days of onset of symptoms, is a predictor of response. However, response still occurred in patients treated 60 days after the onset of symptoms. In chronic progressive MS, TPE could be a long-term therapy, if shown to be of benefit, with tapering as tolerated.

References [13, 890–912]

*As of October 21, 2012 using PubMed and the MeSH search terms multiple sclerosis and plasma exchange or plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

MYASTHENIA GRAVIS

Incidence: 1/100,000	**Condition**	**Procedure**	**Recommendation**	**Category**
	Moderate –severe	TPE	Grade 1B	I
	Prethymectomy	TPE	Grade 1C	I

# of reported patients*: >300

	RCT	**CT**	**CS**	**CR**
Moderate - severe	8 (279)	7 (2802)	30 (556)+	NA
Prethymectomy	0	5 (342)	2 (51)+	NA

+6(405) case series contained both groups of patients; CS includes anti-MuSK 1(10) and with rippling muscle disease 2(10).

Description of the disease

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 20–40 year old women. The causative antibody is usually directed against the acetylcholine receptor (anti-AChR) on the postsynaptic surface of the motor end plate. Ordinarily, motor nerves release the neurotransmitter acetylcholine (ACh) at the neuromuscular junction. The neurotransmitter crosses the synaptic space to the muscle surface where it binds the AChR and stimulates an action potential and muscle contraction. Anti-AChR reduces the number of available acetylcholine receptors, thus decreasing the action potential achieved with stimulation; 80–90% of MG patients have detectable anti-AChR. Other factors might play a role in the disease as antibody level does not correlate with disease severity; severe disease can occur without detection of the antibody. Approximately 50% of anti-AChR seronegative disease is due to antibodies to the muscle specific receptor tyrosine kinase (MusK). MuSK mediates formation of the neuromuscular junction and induction of the AChR. The remainder of seronegative individuals may have these antibodies at levels undetectable using current laboratory methods, or they may have other autoantibodies that act 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. Thymic abnormalities, such as hyperplasia or thymoma, are commonly associated with MG.

Current management/treatment

With modern treatment regimens the mortality from MG has greatly decreased from 30% to less than 5%. The four major treatment approaches include cholinesterase inhibitors, thymectomy (anti-MUSK antibody positive patients respond less often than anti-AChR positive patients), immunosuppression, and either TPE or IVIG. Cholinesterase inhibitors (e.g., pyridostigmine bromide) delay the breakdown, and increase the availability, of ACh at the motor end plate and lead to variable improvement in strength. Cholinergic side effects, including diarrhea, abdominal cramping, increased salivation, sweating and bradycardia, can be dose limiting and lead to noncompliance. Thymectomy leads to clinical improvement in many patients under the age of 65 years but it may take years for the benefits to show. Immunosuppressive drugs (corticosteroids, azathioprine, cyclosporine, and tacrolimus) have a delayed effect and therefore play an important role in long-term rather than short-term management.

Rationale for therapeutic apheresis

TPE is used principally to remove circulating autoantibodies, although both seropositive and seronegative patients respond to TPE. TPE is especially used in myasthenic crisis, perioperatively for thymectomy, or as an adjunct to other therapies to maintain optimal clinical status. TPE works rapidly; clinical effect can be apparent within 24 h but may take a week. The benefits will likely subside after 2–4 weeks, if immunosuppressive therapies are not initiated to keep antibody levels low. TPE may be more effective than IVIG in patients with MuSK related MG. TPE may be more effective if initiated earlier in the hospital course.

Three randomized controlled trials (RCT) as well as other comparative effectiveness studies have compared IVIG and TPE. One trial randomized 87 patients with major exacerbations to 3 every other day 1.5 volume TPE, 0.4g/kg/day × 3 days of IVIG, or 0.4g/kg/day × 5 days of IVIG. All three arms were equivalent at day 15. A second RCT that included 12 stable patients with moderate to severe disease found TPE to be better at 1 week, equivalent improvement at 4 weeks, and neither to show improvement at 16 weeks. A third RCT included 84 worsening moderate to severe patients treated with IVIG (1 g/kg/day × 2 days) or TPE (1 TPV for 5 exchanges performed every other day). Improvement at day 14 was equivalent (69% on IVIG and 65% with TPE, and 18% worsened on IVIG and 2% with TPE). One comparative effectiveness study demonstrated IVIG to be more cost effective with shorter length of stay than TPE, but have comparable outcomes. Notably in this study patients who received TPE versus IVIG were more likely to be intubated and have respiratory failure prior to initiating treatment. Thus, IVIG and TPE appear equivalent in the literature.

In addition, RCT showed daily to be equivalent to every-other-day small volume exchanges (20–25 mL/kg). Clinical trials have reported on the use of TPE prior to thymectomy: most studies have shown improved patient outcome with routine use of TPE but other studies have shown equivalent outcomes with selective TPE use in patients at high-risk for postprocedure prolonged intubation.

Technical notes

Volume treated: 1–1.5 TPV	**Frequency:** Daily or every other day
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

A typical induction regimen consists of processing 225 mL/kg of plasma over a period of up to two weeks but smaller volumes process can be beneficial. The number and frequency of procedures depends upon the clinical scenario. Some patients may require long-term maintenance TPE.

References [913–926]

*As of July 18, 2012 using PubMed and the MeSH search terms myasthenia gravis and plasmapheresis and plasma exchange for articles published in the English language. References of the identified articles were searched for additional cases and trials.

MYELOMA CAST NEPHROPATHY

Incidence: 1/100,000/yr	**Procedure** TPE	**Recommendation** Grade 2B	**Category** II
# of reported patients*: 100–300			
RCT	**CT**	**CS**	**CR**
5 (182)	0	8 (102)	7 (10)

Description of the disease

Renal disease 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 pathological distal tubule cast formation focus on an increase in light chain concentration in the distal tubular urine. This may result from the overwhelming of proximal tubule processing of light chains when light chain production is rising due to tumor progression. Other contributing factors may include hypercalcemia, hyperuricemia, dehydration, intravenous contrast media, toxic effects of light chains on distal tubular epithelium, etc.

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) in order to solublize positively charged light chains. Antimyeloma chemotherapy consisting of an alkylating agent with a corticosteroid is used to diminish M-protein production. More recently, immune modulation (thalidomide, lenalidomide) and proteasome inhibition (bortezomib) have emerged as effective therapy**.** Supportive care with hemodialysis or peritoneal dialysis is employed as needed.

Rationale for therapeutic apheresis

Although chemotherapy and alkaline intravenous fluid are the primary modes of therapy, TPE has been used to acutely decrease the delivery of light chains to the renal glomerulus for filtration. Peritoneal dialysis (but not hemodialysis) can also remove light chains but with lower efficiency than TPE. A randomized trial of 21 patients with biopsy-proven myeloma kidney (cast nephropathy) who received melphalan, prednisone and forced diuresis with or without TPE showed no statistically significant outcome differences. However, among a dialysis-dependent subgroup, 43% in the TPE group and none in the control group recovered renal function. In particular, biopsy findings that indicated potential reversibility (e.g., absence of fibrosis of all affected glomeruli) were important predictors of success. This led to an endorsement of TPE for myeloma kidney by the Scientific Advisors of the International Myeloma Foundation. The largest randomized trial of chemotherapy and supportive care with or without TPE failed to demonstrate that 5–7 TPE procedures over 10 days substantially reduces a composite outcome of death, dialysis dependence or estimated glomerular filtration rate of <30 mL/min/1.73 m^2 at 6 months. This study has called into question the role of TPE in the treatment of myeloma kidney in an era of rapidly effective chemotherapy. On the other hand, this study has been criticized in that most of the enrolled patients were not proven to have cast nephropathy by renal biopsy, confidence intervals were wide, suggesting the study was underpowered, and the composite outcome undervalued an end result of dialysis independence for many patients. Survival at six months, as opposed to end points more specific to recovery of renal function, has also been questioned as part of the composite outcome. More recent data suggest that TPE has only transient effects on serum free light chains as measured using a clinically available assay. Biopsy-proven cast nephropathy may be an important supportive finding if TPE is contemplated.

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.

Technical notes

Initial management, especially in the case of nonoliguric patients, should focus on fluid resuscitation (2.5–4 L/day), alkalinization of the urine and chemotherapy. If serum creatinine remains elevated after several days, consider TPE addition. For patients who are oliguric, who excrete $\geq$10 g of light chains per 24 h, or whose serum creatinine is $\geq$6 mg/dL, TPE may be included in initial management, especially in the case of light-chain myeloma. All of the published studies combine TPE with chemotherapy and other forms of supportive care described above. Published studies vary with respect to treatment schedules and replacement fluids employed for TPE. 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	**Frequency:** Daily or every other day
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

Controlled trials have employed TPE as a short-term adjunct to chemotherapy and fluid resuscitation over a period of 2–4 weeks. In some studies and reports, a course of TPE, (10–12 procedures over 2–3 weeks) may be repeated depending on the patient's clinical course.

References [927–949]

*As of October 14, 2012, using PubMed and MeSH search terms multiple myeloma, renal disease and apheresis for journals published in the English language. References of the identified articles were searched for additional cases and trials.

NEPHROGENIC SYSTEMIC FIBROSIS

Incidence: Rare	**Procedure**	**Recommendation**	**Category**
	ECP	Grade 2C	III
	TPE	Grade 2C	III

# of reported patients*:<100

	RCT	**CT**	**CS**	**CR**
ECP	0	0	5 (17)	2 (3)
TPE	0	0	5 (11)	1 (1)

Description of the disease

Nephrogenic systemic fibrosis (NSF) is a rare but severe systemic disorder seen in patients with acute or chronic kidney disease, which has been almost exclusively associated with the administration of gadolinium (Gd) containing contrast agents. It has been reported to occur in 0–18% of patients with renal failure receiving Gd contrast agents, although newer cases have rarely been reported to FDA for the past few years. The highest risk has been identified is GFR <15 mL/min. A large number of cases with chronic kidney disease have been in patients with stage 4 (GFR 10–29 mL/ min/1.73m^2) or stage 5 (dialysis dependent) chronic kidney disease. It has not been seen in those with a GFR >60 mL/min/1.73m^2. The mean time interval between gadolinium administration and NSF onset is 2 days ranging from the same day to 18 months. Higher dose of gadolinium has higher risk than standard dose. NSF has also been seen in patients with hepatorenal syndrome and in the perioperative period following liver transplantation. Additional factors associated with NSF include thromboembolism, surgery, systemic infections, hypercoaguable states, metabolic acidosis, high erythropoietin levels, and elevations in calcium, iron, zinc, copper, and phosphate.

NSF involves the skin and consists of a symmetrical erythematous rash, non-pitting edema, paresthesias, and pruritus involving the extremities. Additional findings may include hair loss, gastroenteritis, conjunctivitis, bilateral pulmonary infiltrates, and fever. Over 6–12 months, the swelling, pruritus, and sensory changes resolve while the skin progresses to a thickened, hardened dermis/subcutis with epidermal atrophy. Fibrosis results in joint contractures leading to wheel chair dependence and may extend into deeper tissues including skeletal muscle, heart, pericardium, pleura, lungs, diaphragm, esophagus, kidneys, and testes. In a small group of patients, the disease progresses rapidly to death within weeks to months while the remaining demonstrate slow progression. In addition, cure is rarely reported. Overall mortality rate can be up to 30% with death due to restricted mobility and respiratory insufficiency.

The pathophysiology of the disorder is uncertain. Advanced kidney disease markedly prolongs Gd contrast excretion. The prolonged elimination results in disassociation of the Gd, which may be further enhanced by metabolic acidosis. Increased phosphate levels and inflammation lead to Gd phosphate tissue deposition. This is taken up by tissue macrophages resulting in pro-inflammatory and pro-fibrotic cytokine production leading to tissue infiltration by circulating CD34+ fibrocytes and collagen production. Gd may also directly stimulate fibroblasts. Multiorgan Gd deposition and fibrosis have been reported in autopsy-based reviews.

Current management/treatment

Replacement of renal function through renal transplant has been associated with cessation of progression and reversal. It should be noted that dialysis has not been associated with improvement once symptoms are established. Delay in initiation of prophylactic hemodialysis shortly after exposure may decrease the possible positive effect. Additional therapies which have been used include steroids, immunosuppression, imatinib messylate, chelation therapy with sodium thiosulfate, phototherapy, plasma exchange, and extracorporeal photopheresis. Avoidance of Gd administration, if possible, has been recommended for patients with GFR <30 mL/min; this has resulted in decreased reports of new cases.

Rationale for therapeutic apheresis

Due to the lack of an effective therapy and similarity between NSF and scleromyxedema, TPE has been applied. Twelve patients treated with TPE have been described in the literature. Seven patients demonstrated improvement including skin softening (7), increased range of motion (ROM) (4), improved ambulation (1) and improvement from wheel chair bound to walking in one patient. Additional reported changes have included decreased swelling, pain, and paresthesias. Decreased transforming growth factor-β1 post TPE has been reported to be associated with clinical improvement.

ECP has been applied to NSF because of similarities to symptoms of chronic graft versus host disease and scleromyxedema. Twenty patients treated with ECP have been described in the literature. Sixteen demonstrated improvement including skin softening (16), increased ROM (12), improved ambulation (4), and improvement from being wheel chair bound to walking in three patients. Additional reported changes have included resolution of skin lesions and decreased pruritus.

Technical notes

Relationship between time of initiation of therapy and reversal of changes is unclear. Whether the changes become irreversible or if earlier treatment is more effective than later has not been determined.

Volume treated: ECP: MNC product typically obtained after processing 1.5 L of blood. The two step process method collects and treats MNCs obtained from 2 TBV processing; TPE: 1–1.5 TPV	**Frequency:** ECP: Various schedules ranging from 2 in consecutive days every 2–4 weeks up to 5 procedures every other day (cycle) with increasing number of weeks between cycles (1–4) with 4 cycles composing a round; TPE: Various schedules ranging from daily for 5 treatments to twice per week for 10–14 treatments
Replacement fluid: ECP: NA; TPE: albumin	

Duration and discontinuation/number of procedures

Time to response has not been reported for most patients treated with TPE. Improvement of early symptoms in one patient reported to have occurred within 3 days of initiation of treatment. Time to response with ECP ranged from 4–16 months. Reports have treated patients for a fixed number of procedures as outlined above.

References [950–966]

*As of August 25, 2012 using PubMed and the MeSH search terms nephrogenic systemic fibrosis or nephrogenic fibrosing dermopathy and apheresis, plasmapheresis, plasma exchange, or photopheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials. This fact sheet includes abstracts in the summary of published reports and considers them in determining the recommendation grade and category.

NEUROMYELITIS OPTICA

Incidence: Rare	**Condition**	**Procedure**	**Recommendation**	**Category**
	Acute	TPE	Grade 1B	II
	Maintenance	TPE	Grade 2C	III

# of reported patients*: 100–300

	RCT	**CT**	**CS**	**CR**
Acute	0	2 (59)	11 (99)	29 (39)
Maintenance	0	0	1 (7)	1 (2)

Description of the disease

Neuromyelitis optica (NMO; Devic's disease) is an inflammatory demyelinating disorder characterized by attacks within the spinal cord and optic nerve. Symptoms of myelitis include paraparesis and sensory loss below the lesion, sphincter loss, dyesthesia, and radicular pain. Symptoms of optic neuritis include ocular pain, visual field deficits, and positive phenomena. Symptoms of hypothalamic and brainstem involvement, which occur in 15% of patients, include hiccups, intractable nausea, and respiratory failure. NMO differs from MS in that it is more typical in nonwhites (African Americans, Asians, and Indians), women (1:4–5 male: female), and has older age of onset. Additional distinguishers from MS are longitudinal spinal cord lesions (3 or more vertebral segments) and an absence of cerebrospinal fluid (CSF) oligoclonal IgG bands but the presence of CSF leukocytosis. In addition, brain MRI is not typical for MS. NMO is associated with other autoimmune diseases, such as SLE, Sjögren's, and myasthenia gravis, as well as viral infections and vaccinations. NMO can have either a monophasic or relapsing course. Monophasic course is associated with younger age at disease onset and equal male:female predominance. Monophasic course has a 90% 5 year survival rate. Approximately 80% of patients with NMO have relapsing course, which has a poor prognosis: 50% of patients become legally blind or wheelchair bound and 30% die with respiratory failure within 5 years. There is not a progressive phase like MS; the disease worsens by incomplete recovery with each acute attack.

Strong evidence suggested that autoantibody against aquaporin-4 (AQP4), the principal water channel on astrocyte foot processes at the blood brain barrier, is pathogenic in NMO. IgG binding to AQP4 may lead to complement-dependent astrocyte cytotoxicity, leukocyte infiltration, cytokine release, and blood–brain barrier disruption, resulting in oligodendrocyte death, myelin loss and neuron death. Histopathology of NMO includes deposition of IgG and complement in the perivascular space with a granulocyte and eosinophil infiltrate, and hyalinization of vascular walls. The detection sensitivity of AQP4 antibody (NMO-IgG) is dependent on the assay used, but one study determined its sensitivity as 91% and specificity as 100% (70% of NMO patients are NMO-IgG positive).

Current diagnostic criteria are: optic neuritis, acute myelitis, and at least two of three supportive criteria: contiguous spinal cord MRI lesions extending over $\geq$3 vertebral segments, brain MRI not meeting diagnostic criteria for MS, and NMO-seropositive status.

Current management/treatment

Acute attacks are managed by high-dose intravenous steroids (usually intravenous pulse steroids (methylprednisone 1 g every 24 h for 5 days followed by oral steroid taper)) and, if symptoms fail to resolve, TPE is added. Relapses are commonly resistant to steroids, and TPE can be helpful in recovery from acute attack. Prophylaxis to prevent further acute attacks includes immunosuppressive medications and immunomodulation, such as rituximab, methotrexate, interferon, azathioprine, cyclophosphamide, prednisone, IVIG mitoxantrone, interferon, and mycophenolate mofetil.

Risk factors for recurrence include Sjögren's' syndrome seropositivity, NMO-IgG seropositivity, female gender, older age (>30 years), less severe motor impairment after the myelitic onset, longer interval between the first and second attack (>6 months) and systemic autoimmunity.

Rationale for therapeutic apheresis

Based on the involvement of NMO-IgG in the pathogenesis of NMO, it is reasonable to postulate that TPE has a role in the treatment of NMO. A number of case reports have shown TPE benefits in corticosteroid-refractory NMO exacerbation. One nonrandomized control study showed TPE as an add-on treatment to pulsed intravenous corticosteroids is more effective than pulsed intravenous corticosteroids alone in patients with acute optic neuritis and limited forms of NMO. The 16 patients treated with TPE and corticosteroids had greater final visual acuity and less thickness in the temporal quadrant than the 19 patients treated with corticosteroids alone. In addition, retrospective case reviews have shown that TPE may also be beneficial as a chronic treatment for the prevention of NMO relapse. One study determined that men, those who received TPE early after attack (<20 days), and had preserved reflexes were more likely to respond to TPE, but the optimal time to start TPE (including add-on or rescue as well as combination treatment) needs to be determined by future clinical trials. In the retrospective cohort study, those who received TPE had lower residual disability scores. In case series, 50–70% of patients showed improvement after TPE. All patients had received steroids.

Double-filtration plasmapheresis has also been reported to be used successfully to control NMO exacerbation.

Technical notes

Volume treated: 1–1.5 TPV
Replacement fluid: Albumin
Frequency: Acute: daily or every other day; Maintenance: variable

Duration and discontinuation/number of procedures

The majority of studies performed 5 procedures on average for acute NMO exacerbation, but ranged from 2–20 procedures. In one case series, 5 out 7 patients who were on maintenance TPE therapy (3 per week for 2 weeks, 2 per week for 2 weeks, then weekly for 3 to 5 weeks) showed varying degrees of improvement and reduction in the number of NMO exacerbation.

References [775, 967–984]

*As of December 30, 2012, using PubMed and the MeSH search terms neuromyelitis optica and Devic's and myelitis and optic neuritis and plasma exchange and plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

OVERDOSE, ENVENOMATION, AND POISONING

Incidence: Rare	**Condition**	**Procedure**	**Recommendation**	**Category**
	Mushroom poisoning	TPE	Grade 2C	II
	Envenomation	TPE	Grade 2C	III
	Natalizumab/PML	TPE	Grade 2C	III
	Tacrolimus	RBC exchange	Grade 2C	III

# of reported patients*: >300

	RCT	**CT**	**CS**	**CR**
Mushroom poisoning	0	0	10 (296)	4 (4)
Envenomation	0	0	2 (40)	3(3)
Natalizumab / PML	0	0	1 (12)/1(28)$^{+}$	1 (1)
Other compounds	0	0	9 (125)	47 (48)
Tacrolimus	0	0	0	1(1)

$^{+}$potential overlap in reported patients; PML = progressive multifocal leukoencephalopathy.

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 occurs at home, most often involving children under the age of six. 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 GI 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. Fewer 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 (Vd) 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. However, one study showed that higher efficacy of removal is achieved when plasma protein binding is >80% and Vd of less than 0.2 L/kg body wt. 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, benzodiazipines, 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 h) resulted in the best outcomes. There are anecdotal reports on the use of IA to treat poisoning with toxins such as botulin toxin. A few case series highlighted the use of TPE to prevent limb loss in victims of snake bites.

There is increasing number of biological drugs such as monoclonal antibodies (pharmacokinetic half-life typically 10–30 days with potentially longer pharmacodynamic half-life) with rare but potentially serious side effects. The results of a recent study suggest that TPE may be effective in rapidly restoring CNS immune effector responses in natalizumab treated patients, which may benefit patients with serious opportunistic infections such as progressive multifocal leukoencephalopathy (PML) caused by reactivation of the polyomavirus JC.

Some medications have affinity to RBCs (e.g., tacrolimus) and RBC exchange has been successfully tried under those circumstances for a severe case of tacrolimus toxicity.

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. Some venoms also cause coagulopathy and possibly microangiopathy with low levels of ADAMTS13, in which case the use of plasma should be strongly considered.

Volume treated: 1–2 TPV **Frequency:** Daily
Replacement fluid: Albumin, plasma

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 [48, 892–907, 985–1005]

*As of October 1, 2012 using PubMed and the MeSH search terms overdose, poisoning, toxicology, mushroom and apheresis, plasmapheresis, mushroom poisoning, snake envenomation, monoclonal antibodies for articles published in the English language. References of the identified articles were searched for additional cases and trials.

PARANEOPLASTIC NEUROLOGICAL SYNDROMES

Incidence: Rare	**Procedure**	**Recommendation**	**Category**
	TPE	Grade 2C	III
	IA	Grade 2C	III

# of reported patients*: 100–300

	RCT	**CT**	**CS**	**CR**
TPE	0	1 (20)	10 (97)	18 (19)
IA	0	0	1(13)	0

Description of the disease

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 CNS anatomy but an international workshop consensus statement called for a combination of immunohistochemistry and Western immunoblotting for proper diagnosis. *Paraneoplastic cerebellar degeneration* (PCD) may present with symptoms developing over several days in patients with small cell lung, 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 down beating nystagmus may precede the diagnosis of cancer by months to years. *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 antineuronal 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. *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, which recognizes neuronal proteins of 55 and 80 kDa on Western blots. *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. *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 carcinoma and malignant melanoma. Most patients have serum autoantibodies to the retinal photoreceptor protein recoverin. A large number of additional antibodies [generally divided into onconeuronal (e.g., anti-Hu) and antibodies against cell surface or synaptic proteins (e.g., NMDAR)] associated with paraneoplastic syndromes of the central and peripheral nervous systems and the neuromuscular junction have been described and extensively reviewed.

Current management/treatment

Although considered autoimmune, neither immunosuppressive nor antitumor therapy is beneficial in most cases of CNS paraneoplastic neurological syndromes. 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. IVIG (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 those whose symptoms are restricted to the peripheral nervous system. Aggressive immunosuppression early in the course is recommended in patients who are identified prior to a tumor diagnosis or whose tumors do not yet require specific anticancer therapy.

Rationale for therapeutic apheresis

The association of these syndromes with specific CSF and serum antibodies led to the use of immunosuppressive therapy, including TPE, in their management. Most patients treated with TPE have also received immunosuppressive drugs as well as specific anti-cancer therapy. TPE often lowers serum but not CSF antibodies and few patients have had convincing improvement after TPE. 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. Patients with acquired neuromyotonia and antibodies directed against voltage-gated potassium channels (VGKC), or PCD with anti-Tr antibodies may be more likely to respond to TPE, though many of them do not have malignancy. Recent, retrospective case series of five patients with VGKC positive neurological syndromes showed sustained clinical improvement after TPE with other immunosuppressive medication. Two of these patients had history of malignancy (see fact sheet on VGKC). A series of 13 patients with POM or PCD were treated with staphylococcal protein A IA of plasma. There were three complete and three partial neurological remissions; all subsequently relapsed.

Technical notes

TPE cannot be considered standard therapy for autoimmune paraneoplastic neurologic syndromes. Protein A IA, either "on-line" or "off-line" may be employed, particularly for POM, although there is very little published experience.

Volume treated: TPE: 1–1.5 TPV; IA: 500–1000 mL of plasma **Frequency:** TPE: daily or every other day**;** IA: twice weekly
Replacement fluid: TPE: albumin; IA: NA

Duration and discontinuation/number of procedures:

TPE: 5–6 procedures over up to 2 weeks; Protein A IA: twice weekly for 3 weeks.

References [1006–1044]

*As of October 14, 2012 using PubMed and the MeSH search terms Paraneoplastic Syndromes and apheresis for journals published in English language. References of the identified articles were searched for additional cases and trials.

PARAPROTEINEMIC DEMYELINATING NEUROPATHIES

Incidence: MGUS: up to 3% of general population >50 yo; Multiple myeloma: 4–6/100,000/yr

Condition	Procedure	Recommendation	Category
IgG/IgA	TPE	Grade 1B	I
IgM	TPE	Grade 1C	I
Multiple myeloma	TPE	Grade 2C	III
IgG/IgA/IgM	IA	Grade 2C	III

# of reported patients*: 100–300

		RCT	CT	CS	CR
IgG/IgA	TPE	1 (39)#	0	3 (29)	1 (1)
IgM	TPE	1 (39)#	0	6 (102)	3 (3)
Multiple myeloma	TPE	0	0	1(4)	1 (1)
IgG/IgA/IgM	IA	0	0	1(3)	4 (5)

MGUS = monoclonal gammopathy of unknown significance; # = the same trial

Description of the disease

Coexistence of neuropathy and monoclonal gammopathy is a common clinical problem. 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 time of onset, severity, mix of sensory and motor features, and presence or absence of positive symptoms.

Polyneuropathy can be associated with and/or caused by the presence of monoclonal proteins in conditions such as amyloidosis, POEMS syndrome, Castleman's disease, type II cryoglobulinemia (see fact sheet on cryoglobulinemia), multiple myeloma (MM), B-cell lymphoma, chronic lymphocytic leukemia (CLL), and 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, especially IgM-MUGUS. In 50% of IgM-MGUS, IgM acts as a specific auto-antibody is against myelin associated glycoprotein (MAG) in peripheral nerves, by Western blot or ELISA. This specificity has also been seen in WM, CLL, IgG- and 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

The optimal treatment for paraproteinemic demyelinating polyneuropathies is not known. Response to immunopressive 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 carmustine. IVIG at 0.4 g/kg 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 rituximab has been successful in IgM PP with anti-MAG. However, two recent randomized controlled trials cited by Ramchandren failed to show efficacy in despite reductions in antibody levels. 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. In one recent review by Lunn, the effects of immunotherapy (including TPE) were viewed as insufficient for any evidence-based recommendations.

Rationale for therapeutic apheresis

The rationale for TPE is removal of anti-MAG or other antibody. It is suggested (*Cortese*) that TPE is probably more effective for IgA and IgG MGUS-associated polyneuropathy, and not for IgM-MGUS. 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 neuropathy disability score, weakness score, and summed compound muscle action potential. While some measures did not reach statistical significance, the observed differences were clinically significant. Importantly, patients from the sham group who were later crossed to TPE treatment also improved clinically. 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-GM1 antibodies.

Other TA modalities such as DFPP 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 **Frequency:** Every other day
Replacement fluid: Albumin, plasma

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 TPE. If the level of paraprotein is correlative 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 [985, 1045–1047]

*As of January 30, 2013 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.

PEDIATRIC AUTOIMMUNE NEUROPSYCHIATRIC DISORDERS ASSOCIATED WITH STREPTOCOCCAL INFECTIONS; SYDENHAM'S CHOREA

Incidence: Unknown for PANDAS and SC; 1.5–2.5% and 6.6–24% of school-aged children have OCD and tic disorders	**Condition**	**Procedure**	**Recommendation**	**Category**
	PANDAS, exacerbation	TPE	Grade 1B	I
	SC	TPE	Grade 1B	I

# of reported patients*: <100

	RCT	**CT**	**CS**	**CR**
PANDAS	1 (29)	0	0	4 (4)
SC	1 (18)	0	0	0

PANDAS = pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; SC = Sydenham's chorea; OCD = obsessive compulsive disorder

Description of the disease

PANDAS and SC are pediatric post-infectious autoimmune neuropsychiatric disorders. Both share an array of neuropsychiatric symptoms, which typically follow Group-A beta-hemolytic streptococcus (GABHS) infection. Both may have a shared etiopathogenesis. A 2012 report modifying the PANDAS criteria to describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome) may be a step towards a resolution of a controversy regarding etiopathogenesis of these disorders. Some investigators have reported that antibodies produced against GABHS, especially streptococcal M-proteins, cross-react with neurons of the basal ganglia. GABHS infection has been associated with childhood-onset neuropsychiatric disorders in genetically susceptible individuals, such as SC, PANDAS, OCD, tic disorder, Tourette's syndrome, etc. A subgroup of these disorders is identified by the acronym PANDAS, which was first described in 50 children by Swedo et al. in 1998. The five diagnostic criteria for PANDAS include: (1) presence of OCD and/or a tic disorder, (2) prepubertal onset, (3) episodic course with abrupt onset or symptom exacerbations, (4) a temporal association of symptoms with GABHS infection, and (5) association with neurological abnormalities (motoric hyperactivity or choreiform movements). The onset of PANDAS is acute and abrupt, often associated with co-morbid neuropsychiatric symptoms, including mood lability, attention deficit-hyperactivity disorder, oppositional defiant disorder, overanxious disorder, separation anxiety, tactile/sensory defensiveness, enuresis, and catatonia. Severe symptoms often last several weeks to months or longer and then gradually subside. SC, a neuropsychiatric manifestation of rheumatic fever, occurs in about 10–20% of patients with acute rheumatic fever, typically 4–8 weeks after a GABHS pharyngitis. The major clinical manifestations include chorea, hypotonia and emotional lability. SC is self-limiting and resolves after 6–9 months, but up to 50% of cases have persistence and recurrence of symptoms. SC is characterized by rapid, jerky, involuntary muscle contractions of the limbs, face, and trunk. During the choreic episode, more than 60% of children with SC 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, with male predominance in PANDAS (2.6:1) and female predominance in SC (2:1). No laboratory tests that are specific for diagnosis and differentiation of PANDAS and SC. Evidence of GABHS infection through throat culture and/or an elevated or increasing antistreptococcal antibody titer [(e.g., anti-streptolysin O (ASO), antideoxyribonuclease–B (antiDNAse-B)] supports the diagnosis of both. Elevated levels of antineuronal antibodies and/or antibasal ganglia antibodies have been reported in both. MRI studies demonstrated striatal enlargement in basal ganglia, especially in caudate, putamen, and globus pallidus in both. SC is diagnosed exclusively by the presence of chorea and a history of rheumatic fever. In PANDAS, exacerbations of symptoms, at least two episodes of neuropsychiatric symptoms, are temporarily associated with streptococcal infection but is not associated with rheumatic fever. None of 60 children with PANDAS had rheumatic carditis by ECHO. During times of remission, a negative throat culture or stable titers are noted. It is very important to differentiate the two since their treatment can be different. In addition, application of all five criteria to make a diagnosis of PANDAS would prevent unwarranted use of antibiotics in children with OCD or tics.

Current management/treatment

Initial treatments for PANDAS include cognitive behavioral therapy and/or antiobsessional medications. Prompt antibiotic administration is indicated in patients with PANDAS with a tonsillo-pharyngitis and a positive GABHS throat culture. In a double blind, randomized controlled trial, penicillin and azithromycin prophylaxis were found to be effective in decreasing streptococcal infections and symptom exacerbations in 23 children with PANDAS. This study suggested that penicillin prophylaxis might be considered in children with PANDAS and who have ongoing risk of GABHS exposure. However, azithromycin prophylaxis should not routinely be recommended because of emerging resistant streptococci. Tonsillectomy may represent an effective prophylactic treatment option in PANDAS patients, if clinically indicated. Severe form of SC is treated with diazepam, valproic acid, carbamazepine, or haloperidol. If these fail, corticosteroids may be tried. Unlike in PANDAS, children with SC require long-term penicillin prophylaxis to reduce the risk of rheumatic carditis. In severely symptomatic patients with PANDAS or SC, immunomodulatory therapies, such as IVIG (1 g/kg/d for 2 days) or TPE, have been shown to be effective in reducing 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. In two patients with PANDAS, TPE resulted in significant and rapid improvement of OCD symptoms and a simultaneous decrease in basal ganglia swelling on MRI. A randomized placebo-controlled trial of IVIG and TPE on 29 children with PANDAS showed that both therapies at one month after treatment produced striking improvements in OCD, with mean improvement of 45 and 58%, respectively, as well as improvement in anxiety and overall functioning. 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 and tic symptom relief than did the IVIG group. Another 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.

Technical notes

Volume treated: 1–1.5 TPV **Frequency:** Daily or every other day
Replacement fluid: Albumin

Duration and discontinuation/number of procedures

Five or 6 procedures over 7 to 14 days were utilized in the RCT. There are no data on any benefit of repeated treatment.

References [985, 1048–1071]

*As of October 14, 2012 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 of the identified articles were searched for additional cases and trials.

PEMPHIGUS VULGARIS

Incidence: 0.42/100,000/yr (US)	**Condition**	**Procedure**	**Recommendation**	**Category**
	Severe	TPE	Grade 2B	III
	Severe	ECP	Grade 2C	III
	Severe	IA	Grade 2C	III

# of reported patients*: 100–300

	RCT	**CT**	**CS**	**CR**
TPE	1 (40)	0	8 (87)	13 (13)
ECP	0	0	1 (4)	7 (11)
IA	0	0	6 (35)	5 (5)

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. In some reports titers of IgG4 antikeratinocyte antibodies correlated with disease activity.

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 immunosuppresion). 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, ECP, intravenous IVIG therapy, and rituximab, have been investigated. The combination of IVIG and rituximab have been found effective in a case series of 11 patients with refractory disease. In addition, some newer experimental technologies involve cholinergic receptor agonists, desmoglein 3 peptides and a p38 mitogen activated protein kinase inhibitor.

Rationale for therapeutic apheresis

The rationale for using TPE and IA 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. In one small multicenter randomized control trial patients were randomized into prednisolone alone ($n = 18$) and prednisolone plus 10 large volume TPE ($n = 22$) over four weeks. There were four septic deaths in the TPE arm. There was no steroid sparring effect noted in the TPE arm. The patients received significant doses of prednisolone (control arm 4246 ± 1601 mg vs. 5237 ± 5512 mg in the TPE arm). The study, though not powered to answer the question of clinical benefit, underlines the potential side effects of immunosuppressive therapy. IA (not available in the US) has been promoted in Europe with increasing number of patients treated and reported clinical responses. There is an ongoing randomized controlled trial comparing immunotherapy (steroids plus azathioprine/MMF) with or without IA.

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 patients 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: TPE: 1–1.5 TPV; ECP: MNC product of 200–270 mL. The 2-process method collects and treats MNCs obtained from 2-times TBV processing. IA: per manufacturers recommendations
Replacement fluid: TPE: Albumin, plasma; ECP: NA; IA: NA

Frequency: TPE: Daily or every other day;
ECP: two consecutive days (one series) every 2 or 4 weeks; IA: daily up to four days and followed up by various frequency protocols

Duration and discontinuation/number of procedures

For TPE and IA, 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 [296, 1072–1085]

*As of October 14, 2012 using PubMed and the MeSH search terms pemphigus vulgaris and apheresis, plasmapheresis, immunoadsorption, and photopheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

PERIPHERAL VASCULAR DISEASES

Incidence: 3–10% of population (US)	**Procedure** LDL apheresis	**Recommendation** Grade 2C	**Category** III
# of reported patients*: <100			
RCT	**CT**	**CS**	**CR**
0	0	6 (97)	1 (1)

Description of the disease

Peripheral vascular disease (PVD) also known as peripheral arterial disease (PAD) or peripheral artery occlusive disease (PAOD) is a condition with narrowing and hardening of the arteries that supply the legs and feet. It is mostly caused by atherosclerosis resulting in walls of the arteries being stiffer and unable to dilate. This leads to insufficient blood flow. It affects about 3–10% of US population, especially men over age 50. Other risk factors include smoking, diabetes mellitus, dyslipidemia, hypertension, coronary artery disease, renal disease on hemodialysis, and cerebrovascular disease. PAD is a strong risk factor for cardiovascular disease.

Clinical presentation of PAD may be asymptomatic or exhibit claudication (pain, achiness, fatigue, burning, or discomfort in the affected muscles, triggered by walking or exercise and released by resting), pain and cramps at rest and night, ulcers or wounds that are slow to heal or do not heal, noticeable color or temperature change, diminished hair and nail growth on affected limb and digits, impotence, as well as other symptoms. Diagnosis of PAD is made through the ankle brachial pressure index (ABPI/ABI), followed by a lower limb Doppler ultrasound examination for site and extent of atherosclerosis. In addition, angiography, CT scan, and MRI are also used. Pathophysiological factors involving PAD include atherosclerosis, endothelial cell dysfunction, and defective nitric oxide (NO) metabolite physiology and others.

PAD is commonly categorized with the Fontaine stages: stage 1: mild pain when walking (claudication), incomplete blood vessel obstruction; stage 2: severe pain when walking relatively short distances (intermittent claudication), pain triggered by walking "after a distance of >150 m in stage II-a and after <150 m in stage II-b"; stage 3: pain while resting (rest pain), mostly in the feet, increasing when the limb is raised; and stage 4: biological tissue loss (gangrene) and difficulty walking.

Current management/treatment

Management of PAD includes risk reduction, such as smoking cessation, proper management of diabetes, hypertension, and cholesterol, use of antiplatelet drugs, and regular balanced exercise. Cilostazol or pentoxifylline has been used to relieve symptoms of claudication. In severe cases, angioplasty and stent placement of the peripheral arteries or peripheral artery bypass surgery of the leg can be performed.

In Japan, LDL apheresis has been used routinely and approved (10 treatments in less than an 8 week period) by the health ministry to be used in Fontaine's grading system II (intermittent claudication) or higher, or when surgical therapy is unavailable or conventional therapy is not effective.

Rationale for therapeutic apheresis

LDL apheresis can decrease LDL cholesterol, the oxidized LDL, C-reactive protein (CRP), and fibrinogen transiently. Lipid apheresis has been shown to enhance peripheral microcirculation, probably by increasing the production of NO and bradykinin, reducing blood viscosity and adhesion molecules.

One RCT was performed in 48 men with primary hypercholesterolemia and extensive coronary atherosclerosis randomized to receiving either biweekly LDL-apheresis plus simvastatin (21) or simvastatin (21) only (*Kroon*). The arm of LDL-apheresis plus simvastatin had shown decreased intima-media thickness of the carotid artery and prevented increase in the number of clinically significant stenoses in the lower limbs as compared to the control arm. A study of (*Kobayashi*) 28 patients with PAD treated with 10 sessions of LDL apheresis (twice per week for 5 weeks), and a follow-up after 3 months showed overall improvement including 82.1% in foot chillness or numbness, 53.6% in intermittent claudication, and 14.3% in foot ulcer. Another study (*Tsuchida*) demonstrated improvement in physiological parameters such as ABI, maximum tolerated walking distance (MTWD) and clinical symptoms in five patients with PAD treated with LDL apheresis. Another study (*Ebihara*) also showed a significantly enhancement in tissue blood flow of both the head and lower limbs after LDL apheresis treatment in 18 patients. Similarly, clinical improvement (absolute walking distance and ABI) was observed in 10 of 19 patients treated with 10 session of LDL apheresis (*Tsurumi-Ikeya*).

Technical notes

Six selective removal systems are available. These are: (1) IA: columns containing matrix bound sheep anti-apo-B antibodies, (2) dextran sulfate columns: remove apo-B containing lipoproteins from plasma by electrostatic interaction, (3) heparin extracorporeal LDL precipitation (HELP): 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 polyacrlyaminde beads, (5) dextran sulfate cellulose columns: remove apo-B containing lipoproteins from whole blood through electrostatic interactions, and (6) membrane differential filtration: filters LDL from plasma. All have equivalent cholesterol reduction and side effects. Currently, the dextran sulfate plasma adsorption and HELP systems are approved by the FDA.

Angiotensin converting enzyme (ACE) inhibitors are contraindicated in patients undergoing adsorption-based Lipid apheresis. The columns function as a surface for plasma kallikrein generation which, in turn, converts bradykininogen to bradykinin. Kininase II inactivation of bradykinin is prevented by ACE inhibition resulting in unopposed bradykinin effect, hypotension and flushing. This is not seen with the HELP system.

Volume treated: 3000–5000 mL of plasma volume	**Frequency:** Once or twice per week
Replacement fluid: NA	

Duration and discontinuation/number of procedures

Ten treatments in less than an 8 week period have been used.

References [1086–1099]

*As of January 12, 2013 using PubMed and the MeSH search terms LDL apheresis, plasma exchange or plasmapheresis and peripheral vascular diseases for articles published in the English language. References of the identified articles were searched for additional cases and trials.

PHYTANIC ACID STORAGE DISEASE (REFSUM'S DISEASE)

Incidence: Rare	**Procedure**	**Recommendation**	**Category**
	TPE	Grade 2C	II
	LDL apheresis	Grade 2C	II

# of reported patients*: <100

	RCT	**CT**	**CS**	**CR**
TPE	0	0	2 (12)	11 (12)
LDL apheresis	0	0	2 (8)	2 (2)

Description of the disease

Phytanic Acid Storage disease (Refsum's Disease), also known as heredopathia atactica polyneuritiformis, is an autosomal recessive disorder first described by Sigvald Refsum, a Norwegian neurologist, in 1946. 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, and in lipoproteins in the plasma. Clinical consequences are largely neurological including retinitis pigmentosa, peripheral neuropathy, cerebellar ataxia, sensorineural deafness and anosmia. Other manifestations include skeletal abnormalities, cardiac arrhythmia and ichthiosis. The clinical progression is typically slow and gradual with onset of signs and symptoms during the 2nd or 3rd decades of life due to the gradual accumulation of phytanic acid from dietary sources. The most frequent earliest clinical manifestations are night blindness and visual disturbances. Progression of symptoms can lead to retinitis pigmentosa, and possibly loss of sight. Patients with cardiac manifestation may experience arrhythmias, which could be fatal or prompt cardiac transplantation. The specific biochemical basis for the accumulation of phytanic acid in these patients is related to an enzyme defect in phytanoyl-CoA hydrolase.

Current management/treatment

Limiting intake of PA by dietary restriction to 10 mg daily is the cornerstone of therapy. PA comes primarily from animal sources such as dairy, butter, cheeses, meats, and some fish. Diet alone can benefit many patients and lead to reversal of neuropathy and icthiosis. Care is taken to maintain overall general nutrition and caloric intake to avoid 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 with, and thus 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

TPE rapidly reduces plasma PA 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 PA in Refsum's Disease range from 700 to 8000 μmol/L. A number of small case series and isolated reports have described clinical improvements in patient signs and symptoms with TPE in conjunction with dietary control. TPE has been found to improve the polyneuropathy, ichthiosis, ataxia, and cardiac dysfunction in most but not all patients treated. Unfortunately, as is also reported with dietary treatment alone, the visual, olfactory, and hearing deficits do not respond. Patients may experience severe exacerbations of disease during episodes of illness or weight loss, such as during the initiation of dietary management. PA levels increase dramatically, possibly due to mobilization of PA stored in adipose tissue. Most authors have used TPE to treat such episodes with marked rapid improvement in symptoms. Chronic TPE strategies have been described which attempt to deplete PA stores following initiation of dietary therapy or to allow for less restrictive diets. Since PA is also bound to plasma lipoproteins and triglycerides, successful management of PA levels with LDL apheresis using double-membrane filtration or dextran sulfate plasma perfusion LDL apheresis has been reported in two case reports and two case series totaling eight patients. The efficiency of PA removal was found to be equivalent to TPE but with less IgG loss. In one case series, patients were treated for as long as 13 years with weekly to biweekly LDL apheresis resulting in lowering of phytanic acid levels, improvement in nerve conduction studies, and stabilization of vision.

Technical notes

Although approaches to therapeutic apheresis for Refsum's Disease vary, a typical course consists of 1–2 TPE per week for several weeks to a month. In some cases, maintenance plasma exchanges continue with decreasing frequency over subsequent weeks to months. When LDL apheresis has been used for chronic therapy, treatments have been weekly to every other weekly.

Volume treated: TPE: 1–1.5 TPV; LDL Apheresis: 3 L
Replacement fluid: TPE: albumin; LDL Apheresis: NA
Frequency: Daily for acute exacerbation; variable for chronic therapy

Duration and discontinuation/number of procedures

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. If chronic therapy is initiated, procedures should be performed life-long.

References [1100–1120]

*As of April 25, 2012 using PubMed and the MeSH search terms Refsum's or phytanic acid and apheresis or plasma exchange or plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

POLYCYTHEMIA VERA AND ERYTHROCYTOSIS

Incidence: PV:1.4/100,000/yr	**Condition**	**Procedure**	**Recommendation**	Category
Prevalence: PV: 22/100,000;	PV	Erythrocytapheresis	Grade 1B	I
secondary erythrocytosis: 0.3%	Secondary erythrocytosis	Erythrocytapheresis	Grade 1C	III

# of reported patients*: >300

	RCT	**CT**	**CS**	**CR**
PV	0	2 (205)	5 (579)	0
Secondary erythrocytosis	0	29	5 (267)	1(1)

PV = polycythemia vera

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 disease (MPD) polycythemia vera (PV), in which an abnormal HSC clone autonomously overproduces red cells. Additional features of PV include splenomegaly, granulocytosis, thrombocytosis and mutations of the tyrosine kinase *JAK2* gene (>90% of cases). 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), Epo augmentation (e.g., postrenal transplantation) or without a primary disorder or features of PV (i.e., idiopathic erythrocytosis). Whole blood viscosity increases significantly as the Hct level exceeds 50%. Symptoms of hyperviscosity include headaches, dizziness, slow mentation, confusion, fatigue, myalgia, angina, dyspnea and thrombosis.

Patients with elevated Hct also have altered blood flow rheology that pushes the platelets (which normally travel at the edges of the vessel) to a narrower flow path, increasing vessel wall and VWF interaction, and may lead to an increased risk of thrombosis. Studies have shown that thrombosis may be due to altered antifibrinolytic activity, endothelial dysfunction and platelet function. Patients may experience major arterial cerebrovascular or cardiovascular thromboembolic events, DVT, PE or intra-abdominal venous events. Roughly 15–40% of patients with PV develop arterial or venous thrombosis. Thrombotic risk factors with PV include uncontrolled erythrocytosis (Hct >55%), 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 CNS.

Current management/treatment

Management of low risk PV includes phlebotomy, often with the goal to maintain the hematocrit at ≤45% and low dose aspirin. Chronic phlebotomy results in iron deficiency, which decreases red cell overproduction. In PV with associated extreme thrombocytosis (platelet count >1,000 × 10^9/L), acquired von Willebrand syndrome (AVWS) and bleeding are additional risks. Aspirin therapy should therefore be avoided in patients with AVWS and a ristocetin cofactor activity <30%. High risk patients, especially those >60 years of age or with a history of a prior thromboembolic event, are treated with phlebotomy, aspirin and cytoreductive agents, such as hydroxyurea. For those patients in whom hydroxyurea is ineffective, other treatments such as busulfan and IFN-α may be considered.

For patients with secondary erythrocytosis, treatment of the underlying cause is preferred. Erythrocytosis due to pulmonary hypoxia may 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 an underlying disorder cannot be reversed, symptomatic hyperviscosity can be treated by isovolemic phlebotomy.

Rationale for therapeutic apheresis

RBC reduction by automated apheresis (erythrocytapheresis), like isovolemic phlebotomy, corrects hyperviscosity by lowering the Hct, which reduces capillary shear, increases microcirculatory blood flow and improves tissue perfusion. Optimal tissue oxygenation also 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 thrombotic complications in a PV patient with Hct >55%. Recently a number of studies have been published supporting the use of erythrocytapheresis as maintenance. A study by Rusak et al. of 76 PV patients found platelet function improvement, as measured by thromboelastography (TEG), after erythrocytapheresis, suggesting that the hemodilution achieved with the procedure may reduce thrombotic risk. A retrospective cohort of 98 patients by Vecchio et al. (6 with PV, 92 with secondary erythrocytosis) observed that chronic automated erythrocytapheresis allowed significantly greater treatment intervals (median 135–150 days; range 2–7 months) to maintain the target Hct compared to chronic phlebotomy (median 40 days; range 20–60 days). A study by Choe et al. employeed double red cell erythrocytapheresis using the Alyx instrument (Fenwal) traditionally used for donor collections and showed improved removal of red cells compared to standard phlebotomy in 158 patients (129 had PV). Decisions to use an automated procedure over simple phlebotomy remain based on clinical necessity, cost and consideration of the risk of adverse events that may be associated with automated procedures. Thrombocytapheresis, as well as erythrocytapheresis, may be indicated for patients with PV and an acute thrombohemorrhagic event associated with uncontrolled thrombocytosis and erythrocytosis.

Technical notes

Automated instruments allow the operator to choose a postprocedure Hct level and calculate the volume of blood removal necessary to attain the goal. A study found that using exchange volume <15 mL/kg and inlet velocity <45 mL/min, especially for patients >50 years may decrease adverse events (*Bai*). Saline boluses may be required during the procedure to reduce blood viscosity in the circuit and avoid pressure alarms.

Volume treated: Volume of blood removed is based on the total blood volume, starting Hct and desired postprocedure Hct. **Replacement fluid**: Albumin	**Frequency:** As needed for symptomatic relief or to reach desired Hct (usually one)

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 [627, 1121–1137]

*As of October 20, 2012 using PubMed and the MeSH search terms erythrocytosis, polycythemia vera, erythrocytapheresis, apheresis, hyperviscosity, myeloproliferative disorder and myeloproliferative neoplasm for reports published in the English language. References of the identified articles were searched for additional cases and trials.

POLYNEUROPATHY, ORGANOMEGALY, ENDOCRINOPATHY, M PROTEIN AND SKIN CHANGES (POEMS)

Incidence: Rare	**Procedure** TPE	**Recommendation** Grade 1C		**Category** IV
# of reported patients*: <50				
	RCT	**CT**	**CS**	**CR**
Myeloproliferative neoplasms	0	0	1(30)	4(4)

Description of the disease

POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, M protein and Skin changes), also known as Crow-Fukase syndrome, Takatsuki disease, is a rare multisystemic paraneoplastic syndrome usually caused by an underlying plasma cell dyscrasia which usually presents in the 5th or 6th decade. The major clinical feature is a chronic progressive polyneuropathy with a predominant motor disability. There are associated features that are not included in the acronym including sclerotic bone lesions, Castleman disease, papilledema, thrombocytosis, peripheral edema, ascites, effusions, polycythemia, fatigue and clubbing. In order to make the diagnosis, a patient should have both of the major criteria: polyneuropathy and monoclonal plasma cell disorder; plus one minor criteria: sclerotic bone lesions, Castleman's disease, organomegaly, edema, endocrinopathy, skin changes or papilledema. Patients usually present with peripheral neuropathy that involves the motor and sensory nerves and can progress to severe weakness. The disease has a chronic course and median survival is approximately 14 years. Differential diagnosis of POEMS includes monoclonal gammopathy of undetermined significance (MGUS)-associated neuropathy, chronic inflammatory demyelinating neuropathy (CIDP), primary systemic amyloidosis, and cryoglobulinemia.

Increased level of cytokines including IL-1β, TNF-α, IL-6 and VEGF appear to play a pathogenic role in the disorder. Specifically, VEGF levels are most frequently elevated and may decrease with successful therapy. VEGF secretion from plasma cell and platelets can lead to vascular permeability, angiogenesis, monocyte/macrophage migration, potentially resulting in arterial obliteration. VEGF release from aggregated platelets has been demonstrated in patients with POEMS. Also, elevated levels of matrix metalloproteinase and tissue inhibitor of metalloproteinase (TIMP) have been observed in patients with POEMS. Usually the bone marrow has <5% plasma cells and protein is elevated in the CSF.

Current management/treatment

There are no randomized controlled trials in patients with POEMS. Treatment is not standardized. Correlation exists between treating the underlying plasma cell dyscrasia and clinical improvement. Radiation therapy is effective first line therapy for improvement of the neuropathy in majority of patients who have a single lesion or multiple lesions in a limited area. More than 50% of patients treated with radiation will respond. For widespread lesions, systemic chemotherapy or high-dose chemotherapy and autologous stem cell transplant should be considered if the patient can tolerate the therapy. Alkylator-based therapy (Cyclophosphamide or Melphalan) ± prednisone can result in substantial clinical improvement in up to 40% of patients. The optimal duration of therapy has not been established but based on the multiple myeloma experience, 12–24 months of treatment is reasonable. The use of corticosteroids alone is a temporizing measure and not a definite therapy.

Rationale for therapeutic apheresis

Patients with POEMS frequently receive TPE prior to diagnosis because they are diagnosed initially with CIDP. In the Mayo clinic review of 30 POEMS patients treated with TPE, 16 were treated with TPE alone without improvement. In the 14 patients who received TPE and corticosteroids, the response rate was 20%, which is similar to steroid therapy alone. They concluded that TPE is ineffective therapy for this disorder.

Technical notes

Volume treated: 1–1.5 TPV	**Frequency:** Mostly every other day (no standard)
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

Variable in literature.

References [1138–1145]

*As of October 31, 2012 us using PubMed and the MeSH search terms POEMS and apheresis or plasma exchange or plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

POST TRANSFUSION PURPURA

Incidence: 2/100,000 transfusions	**Procedure** TPE	**Recommendation** Grade 2C	**Category** III
# of reported patients*: <100			
RCT	**CT**	**CS**	**CR**
0	0	1 (3)	15 (23)

Description of the disease

Post transfusion purpura (PTP) is characterized by severe and abrupt onset of profound thrombocytopenia (platelet count $<10 \times 10^9$/L) 5 to 10 days after transfusion of any blood component, usually RBCs, in a multiparous female. Most commonly PTP occurs in HPA-1a negative patients who have preformed alloantibodies against HPA-1a due to immunization during pregnancy or blood transfusion; other platelet alloantibodies have been implicated. It is not clearly understood why sudden thrombocytopenia develops after transfusion. One explanation is the autoantibody recognizes both self and foreign antibodies (i.e., is panreactive). Another explanation is that the soluble platelet alloantigen or platelet microparticles carrying HPA present in the transfused blood component gets adsorbed to GPIIIa on the patient's platelets. This 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 of which are poorly supported by evidence. The detection of antibodies (generally high titer) against HPA-1a, or other platelet antigen, in a patient's serum that lacks this antigen is necessary for the diagnosis of PTP. The high titer antibody can be detected for up to one year after the PTP episode. PTP is self-limited, with complete recovery in untreated patients in about 20 days. The mortality of PTP is 5 to 10%. Sometimes, especially after cardiac surgery, PTP patients can be falsely diagnosed as heparin-induced thrombocytopenia (HIT) in the early stages. One distinction, however, is that patients with HIT versus PTP do not tend to have a platelet count of $<20 \times 10^9$/L and do not bleed. PTP recurrence after future transfusion is uncommon.

Current management/treatment

The current mainstay of the treatment for PTP is administration of high dose IVIG (0.4g/kg/day for 2 to 5 day or 1 g/kg/day for 2 days), with a 90% response rate. IVIG possibly acts by blocking the Fc receptor of the reticuloendothelial system. All nonessential transfusions of blood components should be immediately discontinued. A bleeding patient should be transfused with alloantigen negative platelets, if available. Alloantigen positive platelet transfusion is generally ineffective and may stimulate more antibody production. However if the patient is actively bleeding, platelet transfusion may decrease bleeding tendencies. High doses of corticosteroids are used, but appear not to change the disease course. In the recent literature, TPE or splenectomy is used only if IVIG, steroids, and platelet transfusion are not effective and severe thrombocytopenia persists.

Rationale for therapeutic apheresis

Removal of platelet alloantibodies by TPE decreases the antibody titer and removes unabsorbed alloantigen; thereby, increasing platelet survival and reversing the bleeding risk. Based on the limited case reports, TPE seems to shorten the duration of thrombocytopenia. TPE should be considered as the urgent treatment of hemorrhage and severe thrombocytopenia if IVIG or other therapies are not effective.

Technical notes

Due to severe thrombocytopenia, the AC ratio should be adjusted accordingly. 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.

Volume treated: 1–1.5 TPV	**Frequency:** Daily
Replacement fluid: Albumin, plasma	

Duration and discontinuation/number of procedures

TPE can be discontinued when platelet count starts increasing ($>20 \times 10^9$/L) and noncutaneous bleeding stops.

References [929, 1146–1151]

*June 1, 2012 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.

PSORIASIS

Incidence: 60–100/100,000; Caucasian >African-Americans	**Condition**	**Procedure**	**Recommendation**	**Category**
		TPE	Grade 2 C	IV
	Disseminated pustular	Adsorptive cytapheresis	Grade 2 C	III
		Lymphocytapheresis	Grade 2 C	III
		ECP	Grade 2 B	III

# of reported patients*: 100–300

	RCT	**CT**	**CS**	**CR**
TPE/cascade apheresis	0	1 (6)	3 (23)	0
Adsorptive cytapheresis	0	0	4 (25)	1 (2)
Lymphocytapheresis	0	0	3 (18)	0
ECP	0	1 (52)	2 (12)	0

Description of the disease

Psoriasis is a chronic skin disorder with a high genetic predisposition. The plaques and papules are a result of hyperproliferation and abnormal differentiation of the epidermis which leads to its thickening (acanthosis). Inflammatory infiltrate consisting of dendritic cells, macrophages, and T cells in the dermis and neutrophils with some T cells in the epidermis contributes to the overall thickness of the lesions (from thin- to thick-plaque spectrum). Increased number of tortuous capillaries leads to redness of the lesions. Inheritance of psoriasis is complex, with at least 9 chromosomal loci called psoriasis susceptibility (PSORS) being involved (e.g., PSORS1 is located within MHC region on chromosome 6p21). Some clinical presentations are strongly associated with PSORS (e.g., guttate psoriasis with PSORS1). The disease process involves upregulation of Th1 and Th17 pathways with the transport of T cells from the dermis into the epidermis being a key event. Psoriatic T cells predominantly secrete interferon-γ and interleukin-17. The imbalance is further affected by a decrease in activity but not number of T reg and decreased levels of IL-10. The recirculation of the T cells in the skin leads to keratinocyte proliferation. This interplay between keratinocytes, dendritic cells, lymphocytes and cytokines plays instrumental role in psoriasis and contribution to the disease process of each element is being currently elaborated.

The described clinical types of psoriasis are plaque, guttate, pustular, inverse, nail and erythrodermic. Except for widespread pustular or erythrodermic psoriasis the disease rarely causes death, though with high prevalence hundreds of deaths are reported annually. Clinical response is often evaluated using Psoriasis Area and Severity Index (i.e., PASI score) which evaluates 3 features of the psoriatic plaque (redness, scaling and thickness) and extent of involvement of each body area. The PASI score ranges from 0 to 72, with the highest score describing the worst disease presentation.

Current management/treatment

There are topical and systemic therapies for psoriasis. The choice of therapy is generally dictated by the disease severity, comorbidites, and patient's preferences as well as adherence to treatment. The severity of the disease dictates selection of treatment options. Moderate to severe psoriasis is defined as 5–10% involvement of the body surface area. The therapies can be topical such as mollients, corticosteroids, topical vitamin D analogs (e.g., calcipotriene, calcitriol), topical retinoids, topical calcineurin inhibitors (e.g., tacrolimus, pimecrolimus) and currently less popular tar. Different modalities of ultraviolet light are used and include phototherapy (UVB light ± tar), narrow band UVB, photochemotherapy (PUVA, oral or bath psoralen followed by UVA radiation) and excimer laser.

Systemic therapies include methotrexate, retinoids, systemic and calcineurin inhibitors (e.g., cyclosporine). Recently, biologic agents are used more frequently. TNF-alpha inhibitors [etanercept (Enbrel), infliximab (Remicade) and adalimumab (Humira)] and ustekinumab (Stelara), human monoclonal antibody against IL-12 and IL-23, was approved for treatment of moderate and severe psoriasis. Future therapies are likely to be directed against Th17 pathway and monoclonal antibodies directed against IL-17 or IL-17 receptor are being evaluated in clinical trials.

Rationale for therapeutic apheresis

The methodology and rationale for different apheresis procedures has evolved with better understanding of the pathophysiology. A few small studies showed that TPE provides no benefit in the treatment of psoriasis. The rationale for these studies was the removal of the cytokines and putative "psoriatic factor", which at that time were considered contributory to the disease process. With better understanding of the pathophysiology plasma exchange is unlikely to be successful and utilized.

The selective removal of leukocytes through adsorptive granulocyte and monocyte apheresis (e.g., granulocyte/monocyte column) provides for a reasonable pathophysiological justification especially in the context of disseminated pustular psoriasis. In a recent study 15 patients received 5 treatments (one session per week) in addition to standard therapy. There was 85.7% response rate, though the contribution of apheresis is difficult to discern as other therapies were used concurrently. Several smaller studies confirmed improvement in clinical symptoms. The use of lymphocytapheresis was described in several small studies. The rationale for its use is similar to described above. The reported response rate was similar to that shown with adsorptive granulocyte-monocyte columns. Lymphocytapheresis may have a similar effect to adsorptive column but no direct comparison study was reported. However, the apheresis treatment could be only considered in highly selected group of patients with disseminated disease and lack of response to other systemic treatments.

Better understanding of pathophysiology of psoriasis suggests that ECP might be used in its treatment. Large controlled study with 52 patients in the treatment arm (4 two stage ECP treatments) showed statistically significant improvement in PASI scores. Several smaller studies showed variable response.

Technical notes

The granulocyte-monocyte adsorptive columns are not available in the US.

Volume treated: Adsorption: 1,500–2,000 mL; Lymphocytapheresis: 1,500–5,000 mL (1 TBV); ECP: 1,000–3,000 mL (method dependent)
Replacement fluid: Adsorption: NA; Lymphocytapheresis: NA; ECP: NA

Frequency: Adsorption: once a week; Lymphocytapheresis: once a week; ECP: once to twice a week

Duration and discontinuation/number of procedures

Adsorptive columns and lymphocytapheresis are generally used for 5 weeks (total of 5 treatments). ECP has been used for different length of time (2–12 weeks) hence needs to be adjusted based on the patient's presentation as well as the objective of the treatment.

References [1152–1167]

*As of February 9, 2013 using PubMed and the MeSH search terms psoriasis and plasmapheresis, plasma exchange, apheresis, and photopheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

RED CELL ALLOIMMUNIZATION IN PREGNANCY

Incidence: 100/100,000 newborns/yr in US	**Condition** Prior to IUT availability	**Procedure** TPE	**Recommendation** Grade 2C	**Category** III
# of reported patients*: >300				
RCT	**CT**	**CS**		**CR**
0	0	13 (307)		22 (24)

IUT = intrauterine transfusion.

Description of the disease

Hemolytic disease of the fetus and newborn (HDFN, also term erythroblastosis fetalis or hemolytic disease of the newborn) occurs when maternal plasma contains an alloantibody against a RBC antigen carried by the fetus. The maternal IgG crosses the placenta and causes hemolysis of the fetal RBCs. This leads to fetal anemia and when severe enough, hydrops fetalis and/or fetal death. Most frequently severe HDFN is secondary to anti-D (previously termed Rh disease) but it can be caused by a variety of RBC alloantibodies (e.g., anti-K, anti-C, anti-PP1Pk, and anti-E). Sensitization to RBC antigens usually occurs after fetomaternal hemorrhage during pregnancy or delivery, or through previous RBC transfusion. Only 0.1 mL of fetal RBCs can result in Rh sensitization. The severity of HDFN usually increases with subsequent pregnancies. Due to the routine use of prophylactic Rh immunoglobulin during pregnancy and postpartum, the incidence of HDFN secondary to anti-D has greatly decreased.

Current management/treatment

A pregnant woman with a newly identified clinically significant alloantibody is managed by the following. (1) Patient history helps identify the source of exposure, such as previous pregnancy or transfusion. (2) The fetus' father is phenotyped to assess for risk of HDFN, if paternity is assured. If the father does not carry the RBC antigen, then no further work up needs to be performed. If the father is heterozygous for the antigen, the fetus has a 50% chance of also expressing the antigen and being at risk. In order to determine the fetal genotype, amniocentesis at about 15 weeks gestational age is performed or alternatively, in Europe, maternal sampling for fetal genotyping can be performed. If the father is homozygous for the antigen, the fetus is at risk. (3) Maternal antibody titer is performed. For the majority of antibodies (see anti-K below) the higher the titer, the more severe HDFN. Critical thresholds of titers are laboratory dependent, but are typically 8–32. Titers should be repeated with every scheduled prenatal obstetrics visit (approximately monthly until 24 weeks and then every 2 weeks until term). (4) If titers, performed in the same laboratory, are above the critical threshold or have increased by two dilutions from the previous sample, ultrasound should be performed to evaluate the fetus. Ultrasound can detect signs of anemia (middle cerebral artery (MCA) blood flow velocity) and hydrops (ascites), and is a noninvasive method of following the severity of HDFN. Most institutions use ultrasound with MCA measurements initiated as early as 18 weeks gestational age to determine fetal care rather than depend on antibody titration. Once monitoring by ultrasound is initiated serial antibody titration is discontinued. Moderate to severe anemia is predicted when MCA measurement is more than 1.5 multiples of the mean (MoM) for the gestational age. (5) Once this occurs cordocentesis and possible intrauterine transfusion (IUT) is needed. IUT cannot occur until about 20 weeks gestational age. IUT uses RBCs negative for the antigen against which maternal antibody is directed. Fetal mortality related to IUT is 1 to 2%. IUT can be repeated, approximately every 1 to 2 weeks, until the fetus is ready for delivery. (6) Amniocentesis for fetal lung maturity assessment is used to determine if the fetus can be safely delivered. (7) HDFN can result in neonatal hyperbilirubinemia, which can cause kernicterus and permanent brain damage. Therefore, postdelivery the neonate must be closely monitored to prevent and treat hyperbilirubinemia.

Anti-K (Kell) suppresses RBC production as well as causes hemolysis, and antibody titers are not as predictive as other antibodies. Thus, monitoring the MCA blood flow velocity by ultrasound is the preferred method to monitor disease severity.

If the fetus is known to be at high risk for hydrops fetalis based on ultrasound or previous prenatal loss, a more aggressive approach during early pregnancy is warranted. 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 IVIG and/or TPE may be indicated.

Rationale for therapeutic apheresis

TPE removes the maternal RBC alloantibody that causes HDFN. Therefore, TPE will potentially decrease the maternal antibody titer and, in turn, the amount of antibody transferred to the fetus, thereby decreasing RBC destruction and improving HDFN disease course. Survival in severe cases of HDFN with the use of TPE and/or IVIG prior to IUT is about 70%, with cases reported after 2000 having 100% survival. Typically, IUT can be performed after the fetus reaches 20 weeks of gestation.

Technical notes

TPE can safely be performed during pregnancy. Physiologically, blood and plasma volumes increase as the pregnancy progresses. In the second or third trimester, the patient should lay 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.

Volume treated: 1–1.5 TPV	**Frequency:** Three procedures per week
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

TPE should be considered early in pregnancy (from 7 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 (3 procedures) after the 12th week of pregnancy followed by weekly IVIG (1 g/kg) until the 20th week (*Ruma*).

References [1168–1174]

*As of April 16, 2012 using PubMed and the MeSH search terms hemolytic disease of the newborn and red cell alloimmunization and plasma exchange and plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

RENAL TRANSPLANTATION, ABO-COMPATIBLE

Incidence: AMR: 10% renal transplant recipients, 40% renal transplant recipients who underwent desensitization; HLA sensitization: 30% of waiting list patients	**Condition**	**Procedure**	**Recommendation**	**Category**
	AMR	TPE	Grade 1B	I
	Desensitization, LD	TPE	Grade 1B	I
	Densensitization, DD	TPE	Grade 2C	III

# of reported patients*: >300

	RCT	**CT**	**CS**	**CR**
AMR	3 (61)	8 (342)	36 (714)	13 (14)
Desensitization	0	5 (441)	29 (466)	11 (11)
High PRA	0	0	1 (20)	0(0)

AMR = antibody-mediated rejection; LD = living donor; DD = deceased donor

Description of the disease

Renal transplantation is performed to allow individuals with ESRD to discontinue dialysis. Use of immunologically incompatible kidneys is growing due to organ shortage and sensitized candidates- 30% currently wait-listed are presensitized (>80% panel reactive antibodies [PRA]) to Human Leukocyte Antigens (HLA). These HLA antibodies may also be specific towards a prospective donor HLA type (donor specific antigen [DSA]). These HLA antibodies result from blood transfusions, pregnancy, or transplantation and increase risk for graft loss secondary to hyperacute, acute, or chronic AMR. In addition, 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. TPE is now used in many transplant centers, to broaden access to transplantation to (1) patients who have potential living donors with an incompatible crossmatch due to a DSA; (2) patients with high PRA and in need of deceased donor and thus must lower their HLA antibody titer.

AMR has emerged as a leading cause of early and late allograft injury, although still less common than T-cell-mediated cellular rejection. AMR diagnosis is based on the Banff classification and relies on (1) detection of DSA at the time of rejection; (2) histologic evidence of alloantibody-mediated acute inflammation injury, such as glomerulitis and peritubular capillaritis, and (3) staining of the classical complement remnant C4d in peritubular capillaries. Recipients at higher risk of AMR include those with previous transplant and high PRA. Subclinical AMR leads to chronic humoral rejection and late graft loss. For ABO incompatible renal transplantation, see next fact sheet.

Current management/treatment

New immunosuppressive drugs are being developed to prevent and treat acute renal allograft rejection, and to decrease antibody titers. 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 deceased donor 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.

Desensitization regimens to remove DSA typically also include IVIG, rituximab, and/or additional immunosuppression. Less commonly, TPE may continue postoperatively to maintain low antibody levels. (Some series have reported successful transplantation without TPE in the presence of low level DSAs, when flow cross-matches are negative.) Published desensitization protocols use high dose IVIG, TPE or IA, rituximab alone or in combination to convert a positive crossmatch to a negative crossmatch and allow for transplantation. In addition, some case series use other immunosuppressants such as bortezomib. 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. IVIG alone without rituximab and/or TPE has higher AMR rates. Immunosuppressive drugs, such as rituximab, glucocorticosteroids, mycophenolate mofetil, and tacrolimus, are typically initiated at the start of the protocol. Post-transplantation rapid diagnosis and treatment of AMR is essential.

While no regimen is completely effective, several studies have confirmed avoidance of hyperacute rejection and substantial graft survival. In a retrospective review comparing sensitized versus unsensitized patients receiving crossmatch negative deceased donor kidney transplants, sensitized patients had higher rates of graft rejection and graft loss. In this study 20 out of the 73 patients received pretransplantation TPE and/or IA and of these 10 achieved negative PRAs. Outcome was 18% unsensitized group, 41% non-TPE and/or IA sensitized group, 20% TPE and/or IA sensitized group (30% positive PRA at transplant and 10% negative PRA at transplant) graft rejection rate and 5% unsensitized group, 21% non-TPE and/or IA sensitized group, 15% TPE and/or IA sensitized group (20% positive PRA at transplant and 10% negative PRA at transplant) graft loss rate. Therefore, pretransplant TPE and/or IA may decrease graft loss rates in highly sensitized patients receiving deceased donor transplants. One observational study indicated that TPE and low dose IVIG regimens were superior to high dose IVIG in desensitization (*Stegall*), although relatively high rejection rates persisted. Multiple TPE treatments led to more reproducible desensitization. In a recent study of 215 patients who began desensitization treatment, 98% progressed to transplantation (*Montgomery*), and derived a nearly doubling of survival over eight years, compared with others waiting for a compatible organ.

Treatment of AMR has evolved from IVIG-based to combination regimen using TPE, IVIG, and rituximab. Available studies have generally been small and heterogeneous in their protocols, severity, and timing of treatment. Uncontrolled studies have suggested benefit of TPE in the treatment of biopsy-proven acute AMR (*Bartel*), particularly with additional modalities. Clinical trials have demonstrated improved graft survival with TPE+IVIG versus TPE alone or IVIG alone, and TPE + rituximab versus TPE alone. A recent nonrandomized study in AMR compared high-dose IVIG with TPE+IVIG rituximab and showed both better graft survival and lower DSA levels post-transplant with the latter (*Lefacheur*). However the use of rituximab has been associated with increased rates of infection. Only 6.5% of highly sensitized wait-listed patients receive a kidney transplant each year. A recent study concluded that the immunological risk for both AMR and graft loss directly correlate with historical peak DSA strength (*Lefaucheur*). IVIG has limited effectiveness in reducing PRA levels. A recent single-center study suggested that a combination of IVIG and rituximab may be an effective desensitizing regimen (*Vo*). TPE-based regimens appear to be effective only for those awaiting living donor transplants.

Rationale for therapeutic apheresis

In AMR DSA are generated after transplantation. These antibodies can be removed with TPE, DFPP, lymphoplasmapheresis, and IA. Therapeutic apheresis is always in combination with other immunosuppressive drugs, such as antithymocyte globulin, glucocorticosteroids, rituximab, and IVIG. Randomized controlled trials in the early 1980s did not show TPE to be beneficial when used in combinations with corticosteroids for either acute rejection with DSA detected or acute vascular rejection. Case series since 1985 have shown improvement when TPE is used in patients with acute vascular rejection in combination with a variety of antirejection medications. This is likely due to improved antirejection 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 TPE have a graft survival rate of 70–80% (90% in reports with TPE, IVIG, and rituximab).

TPE can also be used prior to transplant to remove HLA antibodies. TPE (some series have used DFPP and one small series used IA) is used in combination with immunosuppressive drugs pre transplant until crossmatch is negative. TPE is usually continued postoperatively also and reinitiated 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. The risk of AMR is approximately 40% with approximately 90% 1-year graft survival. The desensitization protocols should be used only in highly selected patients.

Technical notes

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

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

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 number of treatments based on improvement in renal function and decrease in DSA titers. It is also undecided whether low dose IVIG (100 mg/kg) should be used after every procedure or 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 postoperatively for a minimum of 3 procedures. Further treatment is determined by risk of AMR, DSA titers, or occurrence of AMR.

References [1175–1181]

*As of 10 December 2012 using PubMed and the MeSH search terms antibody mediated rejection, kidney transplant, HLA desensitization and plasmapheresis and plasma exchange for articles published in the English language. References of the identified articles were searched for additional cases and trials.

RENAL TRANSPLANTATION, ABO INCOMPATIBLE

Incidence: Infrequent	**Condition**	**Procedure**	**Recommendation**	**Category**
	Desensitization, LD	TPE	Grade 1B	I
	Humoral Rejection	TPE	Grade 1B	II
	A_2/A_2B into B, DD	TPE	Grade 1B	IV

# of reported patients*: >300			
RCT	**CT**	**CS**	**CR**
0	0	>21 (>755)	28(45)

LD = living donor; DD = deceased donor.

Description of the disease

Due to a relative shortage of compatible organs for transplantation, ABO incompatible (ABOi) living donors are being increasingly used. Major incompatibility refers to the presence of natural antibodies in the recipient against the donor's A or/and B blood group antigen. These antibodies may cause hyperacute/acute humoral rejection of the organ due to endothelial damage (A and B antigens are expressed on vascular endothelium). Minor incompatibility occurs where the organ donor has naturally occurring ABO antibodies against the recipient. Donor lymphocytes present within the graft (known as passenger lymphocytes) may produce antibodies against recipient RBCs resulting in severe hemolysis, although this is relatively uncommon. Major ABOi exists in approximately 35% of random donor–recipient pairs.

Current management/treatment

Based on a recent survey of transplant centers in the US, 24% of programs have performed ABOi renal transplantation, demonstrating that this type of transplantation is being attempted frequently. Most published reports on ABOi solid organ transplants involve TPE-mediated removal of anti-A or anti-B antibodies in conjunction with immunosuppressive treatment with drugs such as tacrolimus, mycophenolate mofetil and prednisone; and monoclonal antibodies such as daclizumab, rituximab, bortezomib and eculizumab. Other immunotherapy modalities including IVIG and antithymocyte globulins (ATG) have important roles in the transplant process. Splenectomy, while formerly considered an absolute requirement for ABOi renal transplantation, is no longer thought to be necessary. However, it continues to be helpful in the setting of refractory rejection after transplantation. Recently published case reports have used rituximab/eculizumab/bortezomib in ABOi renal transplantation, both prophylactically and to treat rejection, but their use varies, and there are no universally accepted protocols for the use of these drugs in this setting. A_1, B, and A_1B donor organs have been successfully transplanted with these desensitization strategies. The natural occurrence of the A_2 blood type, which has reduced expression of A antigen on RBCs and endothelium, has been exploited in transplantation; A_2 donors are preferred over group A_1 donors for group O or B recipients in living donor kidney transplantation as they have a lower risk of graft rejection. A current UNOS variance also permits A_2/A_2B deceased donor kidney transplantation into B recipients if certain antibody titer requirements are met without the need for TPE. Published evidence suggests that outcomes of such transplants are equivalent to ABO-compatible deceased donor transplants.

Rationale for therapeutic apheresis

While there are no controlled clinical trials on using TPE to facilitate ABOi renal transplantation, an abundance of supportive evidence exists. Given that both hyperacute rejection, and acute AMR are definitive risks in ABOi renal transplants, TPE has been used as the key therapeutic modality to reduce anti-A or anti-B antibody titers in the peri-transplant period with the goal of preventing rejection and facilitating graft survival. Retrospective reviews of organ survival data on ABO incompatible transplant patients treated with TPE compare well with ABO compatible transplants. In ABOi kidney transplantation, TPE is used to lower antibody titer below a critical threshold (which differs based on titration method/ technique) prior to the transplant procedure. Therefore, TPE has been included in preparatory regimens for ABOi renal transplantation in addition to different immunosuppressive/immunomodulatory drug therapies. Apart from TPE, specific A or B antigen immunoadsorption columns have been used in Europe to selectively remove anti-A or anti-B antibodies.

Technical notes

The replacement fluid for TPE is albumin with or without use of plasma (plasma should be compatible with both the recipient and donor), depending upon presence or absence of coagulopathy. In the immediate pretransplant setting, plasma or plasma/albumin is typically used.

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

Duration and discontinuation/number of procedures

The goal should be to reduce the antibody titer to less than a critical threshold prior to taking the patient to transplant. It is important to note that this critical titer will need to be determined by each program embarking on this type of transplant, given that titer results can vary widely depending on titration method and technique. The number of TPE procedures required in most reports has depended upon baseline IgG (not IgM) titer, and the efficiency with which ABO antibodies are removed with TPE in the patient. Titers typically increase post-transplantation. Titers in the first 2 weeks post-transplant have a low positive predictive and high negative predictive value for AMR in the setting of ABOi renal transplantation. Most AMR episodes occur within the first 2 weeks following transplantation. Patients should be monitored closely for graft function before discontinuation of TPE. Several ABOi programs utilize protocol biopsies to monitor the allograft for histological signs of rejection prior to discontinuation of TPE. Of note, C4d positivity is very common in ABOi transplant renal biopsies; however this is not necessarily indicative of AMR unless accompanied by light microscopic changes suggestive of AMR.

References [819, 1182–1199]

*As of October 16, 2012 using PubMed and the MeSH search terms ABO incompatible, kidney transplantation, plasma exchange, plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

SCHIZOPHRENIA

Incidence: 25/100,000/ yr	**Procedure**	**Recommendation**	**Category**
	TPE	Grade 1A	IV

# of reported patients*: <100

RCT	**CT**	**CS**	**CR**
1 (10)	0	0	0

Description of the disease

Schizophrenia is a mental illness which is characterized by auditory and visual hallucinations, delusions and thought disorder as well as flattened affect, loss of pleasure and social withdrawal. Schizophrenia affects 1% of the population and is associated with a strong family history. Patients with schizophrenia have a high rate of substance abuse, smoking and suicide.

Current management/treatment

Medical treatment with antipsychotics is the primary treatment. Antipsychotics include dopamine D2 antagonists. Medication should be initiated upon diagnosis. Antipsychotics have multiple neurologic side effects including dystonia, parkinsonism, tremor, and tardive dyskinesia. Newer medications have less neurologic side effects, but have higher metabolic side effects, including diabetes, hypercholesterolemia and weight gain.

Rationale for therapeutic apheresis

Schizophrenia is a chronic psychiatric disorder with psychosis and deterioration in function. The pathogenesis and disease-modifying features of schizophrenia remain undefined but likely represent a complex interaction of genetic, environmental and neurobiological factors. In the early 1980's, it was hypothesized that autoimmunity and endogenous toxigenic substances might play causal roles. Because of this, exploratory trials were carried out to assess the possible beneficial effects of hemodialysis and plasmapheresis. A double-blind, randomized trial of TPE versus sham-apheresis performed on 10 patients demonstrated no benefit.

References [1200, 1201]

*As of June 1, 2012 using PubMed and the MeSH search terms schizophrenia and plasmapheresis, plasma exchange.

SCLERODERMA (PROGRESSIVE SYSTEMIC SCLEROSIS)

Incidence: 19–75/100,000/yr; >8:1 (F:M)	**Procedure**	**Recommendation**	**Category**
	TPE	Grade 2C	III
	ECP	Grade 2A	III

# of reported patients*: >300				
	RCT	**CT**	**CS**	**CR**
TPE	0	3 (75)	6 (60)	18 (19)
ECP	3(162)	0	4 (78)	NA

Description of the disease

Systemic sclerosis (SSc), or scleroderma or progressive systemic sclerosis, is a chronic multisystem disorder of unknown etiology with worldwide distribution characterized clinically by thickening of the skin and by involvement of visceral organs, including the GI tract, lungs, heart, and kidneys. SSc patients present 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 Teleangiectasia). Raynaud's phenomenon is an initial symptom 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. Antinuclear and antinucleolar 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, tenascin, and glycosaminoglycans in skin and other organs is characteristic. 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 among them Th-17 and T regulatory cells and IL-2, increased ratio of circulating CD4 cells to CD8, and significant involvement of macrophages and their products IL-1, IL-6, TNFα, TGFβ, 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 HSC salvage. The role of T cells in pathophysiology leads to increased interest in T cell directed therapies such as halofuginone, basiliximab, alemtuzumab, abatacept and rapamycin. Similarly, experience with rituximab in diffuse cutaneous systemic sclerosis puts B cells as a potential target.

Rationale for therapeutic apheresis

Pathophysiology of SSc as presently understood, lends little support to the use of TPE. 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 reported 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. An effect of long term TPE was evaluated in a controlled trial. The TPE were scheduled as 2–3 weekly for 2 weeks, 1 TPE weekly for 3 months, and 1 TPE every other week as a maintenance therapy. One volume exchange was used with albumin as 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 on 15 patients who received TPE in combination with prednisone and cyclophosphamide, 14 patients had clinical improvement. Severe GI symptoms were ameliorated in 4 patients, severe polymyositis was largely reversed in 2 patients, and pulmonary and cardiac function was improved in others.

ECP has been used in treatment of scleroderma including sham controlled randomized trial of 64 patients. The patients received 2 ECP treatments every month. At the end of 12 months, improvements were observed in skin scores and mean joint involvement in both groups. The study was underpowered and did not reach statistical significance. An earlier multicenter RCT of 79 patients with recent onset and progressive scleroderma also showed improvement in skin and joint parameters at 6 months among those treated with ECP compared to no improvement in those treated with D-penicillamine. Another crossover study of 19 patients revealed no benefit of ECP when skin score or quality of life after 1 year of treatment were evaluated. Recent case series of 16 patients treated with 12 ECP procedures (2 consecutive procedures every 6 weeks) showed decreased number of peripheral Th-17 cells, with values of Tr1 and Treg cells increased, and improved suppressor capacity of Treg cells. Clinical improvement was also observed with decreased dermal thickness and increased joint mobility.

Technical notes

Volume treated: ECP: MNC product of 200–270 mL. The 2-process method collects and treats MNCs obtained from 2-times TBV processing; TPE: 1–1.5 TPV	**Frequency:** ECP: Two procedures on consecutive days (one series) every 4–6 weeks for at least 6 to 9 months; TPE: 1–3 per week
Replacement fluid: ECP: NA; TPE: albumin	

Duration and discontinuation/number of procedures

The length of treatment with TPE varies widely. A course of six procedures over the course of 2–3 weeks should constitute a sufficient therapeutic trial. The treatment with ECP is longer and likely that at least 6 month trial should be considered.

References [1202–1211]

*As of October 1, 2012 using PubMed and the MeSH search terms scleroderma, progressive systemic sclerosis and apheresis, photopheresis, plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

SEPSIS WITH MULTIORGAN FAILURE

Incidence: 300/100,000/yr (US)	**Procedure** TPE	**Recommendation** Grade 2B	**Category** III
# of reported patients*: >300			
RCT	**CT**	**CS**	**CR**
3 (146)	4 (113)	10 (194)	5 (5)

Description of the disease

Sepsis is a systemic inflammatory response to infection in which multiple toxic mediators cause tissue injury, multiorgan dysfunction syndrome (MODS), often with DIC and relative immunosuppression. It is the most common cause of death in noncoronary intensive care units and the 10th most common cause of death in the US. It accounts for 2–3% of all hospital admissions. The incidence of sepsis has increased over the last two decades, and carries a mortality rate of 28–50%; 70% with MODS. 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. Coagulopathy, microvascular occlusion and tissue ischemia appear to be connected to derangements in the balance of ADAMTS13 and VWF multimers.

Current management/treatment

Management includes antimicrobial agents and control of the source of the infection, hemodynamic support including volume and vasopressors, ventilatory support, and avoidance of complications. Additional innovative treatments have included the administration of corticosteroids, monoclonal antibodies to TNF, soluble TNF receptor, antithrombin, and tissue factor pathway inhibitor. These therapies seek to interrupt the cascade of inflammation and coagulation abnormalities.

Rationale for therapeutic apheresis

The rationale for using TPE in sepsis and MODS is to remove pro-inflammatory mediators and, when using plasma replacement, provide anti-inflammatory factors, immunoglobulins, procoagulants and natural anticoagulant proteins as well as ADAMTS13 in an effort to reverse the pathobiological process and restore hemostasis. Because TPE has the potential to remove multiple toxic mediators of the septic syndrome, it may be more effective than blocking single components of the process.

More than 10 nonrandomized studies of TPE in sepsis have found survival rates of 60–87% compared to predicted or historical controls with survival rates of 20–40%. Several case series suggest early treatment is beneficial compared to delayed initiation of therapy. A multicenter cohort study of 23 children with hyperferritinemia and secondary HLH/sepsis/MODS/MAS received either TPE and methyl prednisolone or IVIG (lesser immunosuppressant approach) or TPE and dexamethasone and/or cyclosporine and/or etoposide (higher immunosuppressant approach) and found improved survival (100% versus 50%, $P = 0.002$) with the lesser immunosuppressant approach. There have been studies showing conflicting findings; a prospective cohort of 12 patients with severe sepsis who received 1–5 procedures, pre and post blood level comparisons of inflammatory cytokines TNFα and IL-1β showed no significant change; IL-6 declined over the course of 2–3 procedures.

Three randomized trials of 106, 30, and 10 patients have been published. The largest randomized trial by Busund et al. employed a single TPE with one additional TPE the next day if there was no improvement or hemodynamic instability developed compared to no TPE. They found a 28-day mortality rate of 33% in the TPE group compared to 53.8% in control ($P < 0.05$). Multiple logistic regression used to control for other contributing factors found a decrease in the significance of the effect of TPE on mortality to non-significant trend ($P = 0.07$). A trial by Reeves et al. using continuous plasmafiltration examined 22 adults and 8 children. Although there was no difference in mortality, reduction of some acute phase reactants such as C3, CRP, haptoglobin, and α_1-antitrypsin was achieved. Finally, in the trial by Nguyen et al., 10 children with thrombocytopenia associated multiorgan failure that all were diagnosed with culture positive sepsis were randomized to TPE or standard treatment. Patients in the trial were defined as having low ADAMTS13 if <57% activity. A significant decrease in organ severity scores (PELOD, PEMOD, OFI, $P < 0.001$) and improved 28-day survival (1 of 5 survived in control group, 5 of 5 survived in treatment group, $P < 0.05$) was seen in the TPE treated group who received a median of 12 days of TPEs. Increased ADAMTS13 levels and platelet counts were also seen in the treatment arm. The findings lead to the trial being stopped early due to the interim analysis showing significant improvement in the treatment group.

Technical notes

Both centrifugal based and filtration based apheresis instruments have been used in the trials of TPE. Studies have also employed dialysis techniques combined with apheresis. Patients with or without severe coagulopathy are usually treated with plasma as a replacement fluid. Because these patients are severely ill with hypotension and cardiovascular instability, treatment should be performed in an appropriate setting, such as an intensive care unit.

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; polymyxin B and Matisse columns both bind endotoxin and have been shown to lower mortality or decrease ICU stay in RCTs respectively. These columns were used to treat 1–1.5 blood volumes daily for four days. Neither of these devices has been approved for use in the US.

Volume treated: 1–1.5 TPV	**Frequency:** Daily
Replacement fluid: Plasma	

Duration and discontinuation/number of procedures

The RCT of Busund et al. limited treatment to one to two TPE. The RCT performed by Nguyen et al. performed up to 14 TPE. Case series have treated patients daily until improvement with different endpoints.

References [1212–1239]

*As of November 20, 2012 using PubMed and the MeSH search terms plasma exchange or plasmapheresis and sepsis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

SICKLE CELL DISEASE, ACUTE

Incidence: 289/100,000 African-Americans (1 in 375 for HbSS, 1 in 835 for HbSC, 1 in 1,667 for HbS/β-thalassemia live births); 89.8/100,000 Hispanics primarily from Caribbean islands	**Condition**	**Procedure**	**Recommendation**	**Category**
	Acute stroke	RBC exchange	Grade 1C	I
	Acute chest syndrome, severe	RBC exchange	Grade 1C	II
	Priapism	RBC exchange	Grade 2C	III
	Multiorgan failure	RBC exchange	Grade 2C	III
	Splenic/ hepatic sequestration; intrahepatic cholestasis	RBC exchange	Grade 2C	III

# Reported patients*[+]: >300	**RCT**	**CT**	**CS**	**CR**
Acute stroke	0	1 (52)	7 (160)	8 (10)
Acute chest syndrome	0	1 (40)	13 (145)	8 (8)
Priapism	0	0	1 (5)	1 (1)
Multiorgan failure	0	0	3 (10)	3 (3)
Hepatic sequestration/intrahepatic cholestasis	0	0	1 (52)	3 (4)
Splenic sequestration	0	0	3 (204)	0

[+] The number of reported patients includes patients who received RBC transfusion, manual RBC exchange or automated RBC exchange.

Description of the disease

Sickle cell disease (SCD) affects 90,000–100,000 people in the US. SCD is caused by abnormal hemoglobin (Hb) due to substitution of valine for glutamic acid at β6 (HbS). SCD includes sickle cell anemia, homozygous for the β^s gene (HbSS), as well as HbSC, Hb β-thalassemia (HbSβ^0 and HbSβ^+), HbSD, etc. Morbidity and mortality are significantly higher in HbSS than in other causes of SCDs. HbS polymerizes upon deoxygenation, causing RBCs to become rigid and deformed (sickled RBCs) occluding the microvasculature leading to tissue hypoxia and infarction. Major acute manifestations are vaso-occlusive events (VOEs), splenic sequestration, and transient red cell aplasia (RCA). Painful episodes are the most common VOE. Serious VOEs 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.

Current management/treatment

For acute pain crisis, routine management includes rigorous hydration and pain control.

In the absence of prevention, ischemic stroke can occur in up to 10% (for overt stroke) or 20–35% (for silent stroke) of SCD patients, and with a recurrence rate of 46 - 90%. Patients of HbSS and HbSβ^0 are at the highest risk. Primary and secondary stroke prevention has resulted in marked stroke rate reduction. In SCD patients presenting with weakness/paresis, paralysis, severe headache, mental status change, seizure, sensory deficits, and/or dysarthria/aphasia, urgent CT/MRI should be performed. If stroke is confirmed, emergent RBC exchange should be performed, although data supporting this practice is somewhat limited. A retrospective cohort study (*Hulbert*) showed the rate of recurrent stroke of 57% (8/14) in SCD patients treated with simple transfusion at the time of first stroke, versus the rate of 21% (8/38) of those treated with exchange transfusion (manual or automated exchange), a five-fold greater relative risk.

ACS is defined by sudden decreased PO2 or oxygen saturation despite oxygen therapy in the setting of new infiltrate on chest X-ray, often accompanying fever, tachypnea, coughing, and chest pain. The incident is highest in 2 to 5 year olds. It is likely due to sickling in the pulmonary vascular space. It can be idiopathic, or associated with infection, pulmonary infarction, or fat embolism. The treatment includes supportive care (oxygen therapy, bronchodilator, and mechanic ventilation in severe cases), antibiotics, pain control, and hydration. In addition, transfusion may be indicated (either simple in mild to moderate cases or exchange in severe cases, e.g., oxygen saturation <90% despite oxygen therapy), based on the positive outcome from case reports and series. In addition, the STOP trial (Stroke Prevention Trial in Sickle Cell Anemia) also reported decreased rate of ACS in the transfused SCD patients. However, one study (*Turner*) did not show any differences in outcome comparing simple transfusion versus exchange transfusion (20 vs. 20 subjects).

Priapism (painful sustained erection >4 h) can affect up to 35% of male SCD patients. Treatments include vigorous hydration, pain control, and surgical intervention. It has been reported in small number of case reports and series that RBC exchange has been associated with the resolution of priapism within 24–48 h. Notably, an association of new neurological complications 1–11 days post manual RBC exchange for priapism in 6 SCD boys has been reported, however all of these cases had a significant increase in Hb/Hct post RBC exchange.

Multiorgan failure often involves the lung, liver, and kidney. Management includes timely evaluation and supportive care, in addition, simple or exchange change transfusion may be utilized, as suggested by case reports or case series.

Other acute complications of SCD include hepatic sequestration and intrahepatic cholestasis. In addition to the routine management, hydration and surgical consult, simple or exchange RBC transfusion may be performed.

Splenic sequestration has also been reported to have better outcome in 11 patients (0% mortality) who received either simple transfusion or partial exchange transfusion than historically reported 20% mortality rate (*Rao*).

Rationale for therapeutic apheresis

In severe anemia, simple transfusion is the best transfusion method to improve oxygen-carrying capacity of blood by increasing RBC mass. In acute ischemic stroke, ACS, acute hepatic crisis, or acute life-or organ-threatening complications, RBC exchange is preferred as the HbS concentration is reduced rapidly by replacing RBCs containing HbS with normal RBCs without causing hyperviscosity or volume overload. Additionally, beneficial effects on blood viscosity, elasticity, and relaxation time, and reduction of adhesion molecule level like sVCAM-1 has been documented after RBC exchange.

Technical notes

Apheresis equipment calculates the replacement RBC volume to achieve the desired target HbS (FCR; desired fraction of patient's RBCs remaining at end of procedure) and hematocrit levels. General guidelines to calculate replacement volume using COBE Spectra are: 1) End Hct at 30 ± 3% (≤33–36% to avoid hyperviscosity) and 2) HbS of 30% (or HbS + HbC of 30%, etc). One can assume FCR at 25–40% in remotely transfused/never transfused patients. In recently transfused patients, FCR can be calculated by dividing the desired HbS level by pre-apheresis HbS level multiplied by 100. To maintain isovolemia, primed saline is not diverted and rinseback is omitted at the end of the run. In children, clinically unstable or severely anemic patients, 5% albumin may be used for priming.

Volume treated: Volume necessary to achieve target HbS level	**Frequency:** One procedure to achieve target HbS level
Replacement fluid: HbS negative leukoreduced RBCs and, if available, antigen-matched for at least C, E, and K.	

Duration and discontinuation/number of procedures

For an acute situation, typically one procedure is necessary to achieve desired HbS level (usually <30%) and end Hct (usually 30%).

References [1240–1270]

*As of December 18, 2012 using PubMed and the MeSH search terms sickle cell disease, RBC exchange transfusion, and erythrocytapheresis for articles published in the English language. References of identified articles were searched for additional cases and trials.

SICKLE CELL DISEASE, NON-ACUTE

Incidence: Refer to SCD, acute fact sheet	**Condition**	**Procedure**	**Recommendation**	**Category**
	Stroke prophylaxis/ iron overload prevention	RBC exchange	Grade 1C	II
	Vaso-occlusive pain crisis	RBC exchange	Grade 2C	III
	Pre-Op management	RBC exchange	Grade 2A	III

# Reported patients*+: >300	**RCT**	**CT**	**CS**	**CR**
Stroke prophylaxis/ iron overload prevention	1(130)	0	20(335)	3(3)
Vaso-occlusive pain crisis	1(130)	1(21)	3(18)	1(1)
Pre-Op management	3(1035)	4(184)	3(957)	0

+ The number of reported patients includes patients who received RBC transfusion, manual RBC exchange or machine RBC exchange.

Description of the disease

SCD is described in the sickle cell disease, acute, fact sheet. While infection is the most common cause of death in children (high risk due to defective or absent splenic function), pulmonary hypertension is the most common cause of death in adults. Overall mortality rate for SCD is 2.6% (0.5 deaths/100 person years) with the peak at 1–3 years of age. Average life expectancy now is 50 years or beyond. Chronic complications of sickle cell disease can occur in early age and be life-long. These include chronic/recurrent pain crisis, (VOE), complications from end-organ damage, avascular necrosis of bones, cholelithiasis, complication from chronic transfusions such as iron overload, alloimmunization. In addition, these patients are also at risk for recurrence of severe acute VOEs such as stroke and ACS.

Current management/treatment

Standard therapies for SCD include folic acid to support increased erythropoiesis, pneumococcal, meningococcal and *Haemophilus influenzae* vaccinations and penicillin for infection prophylaxis (these alone have improved lifespan and decreased early mortality), analgesics for painful episodes, and antibiotics for infections. Hydroxyurea (HU) and chronic transfusion are the two main disease modifying treatments options for SCD. As alternatives to HU or chronic transfusion, HSC transplantation from an HLA-identical sibling, partially matched family members or unrelated or related umbilical cord blood unit is an option for patients with first/primary stroke. Even though HSC transplant is the only curative treatment for SCD, it remains under-utilized and its indication and transplant regimens are being defined.

In the STOP trial, SCD children were screened with transcranial Doppler ultrasound (TCD) to detect elevated blood flow velocity that is associated with stroke risk (40% risk in the subsequent 3 years). For patients identified as high risk, they were randomized to standard care without transfusion (control) versus chronic monthly transfusion for primary stroke prevention. For 8.3+/−3.3 years of follow up, there were 10 cerebral infarctions and one hemorrhagic stroke in the control arm (67 patients) and 1 cerebral infarction in the transfusion group (63 patients), $P < 0.001$. In addition, the patients with chronic transfusion also had less ACS and pain crisis. The trial was terminated prematurely due to the marked (90%) risk reduction in primary stroke and the practice of TCD screen in SCD (HbSS and HbSβ^0) and if positive with initiation of chronic transfusion has become the standard care for primary stroke prevention in SCD (*Adams*). Further studies have shown that transfusion withdrawal may be associated with an increased risk of recurrent stroke. In addition, it was reported that the use of 50% pre transfusion HbS may be as effective as 30% pre transfusion HbS (*Cohen*).

Chronic transfusion can result in severe iron overload, which is treated with iron chelation, its effectiveness is limited by poor patient compliance. To avoid iron overload, RBC exchange can be used in lieu of simple transfusion. In one case series with 14 patients receiving chronic exchange transfusion and 7 receiving chronic simple transfusion, exchange transfusion was shown to have reduced iron overload, but increased donor exposure (*Herbert*).

Hydroxyurea can increase the production of HbF. It has been efficacious in reducing frequency of painful episodes, ACS and other severe VOEs, and its use has been associated with less transfusion and hospital admission. It has become the first line chronic management option to reduce moderate to severe pain crisis, in addition to pain medication and optimal hydration. A RCT trial (Stroke With Transfusions Changing to Hydroxyurea, SWiTCH) however failed the attempt to replace chronic RBC transfusions with hydroxyurea and phlebotomy in pediatric patients with severe SCD.

Chronic veno-occlusive pain crises (lasting >3 months) can occur in up to 55% of SCD patients, and the occurrence of pain can happen in up to 9% of days. Case reports have shown improvement in pain crisis after monthly exchange transfusion (manual) in patients with frequent VOE requiring hospitalization. In addition, in STOP trial, pain crisis rate is significantly lower in patients received RBC transfusion (9.7 events per 100 patient-years) versus controls (27.1), $P = 0.014$. Chronic exchange transfusion may be indicated for reducing the occurrence of veno-occlusive pain crises.

High rates (up to 19%) of sickle cell related complication associated with surgery have been reported in SCD patients. One RCT (TAPS study) had demonstrated that pre-op transfusion was associated with decreased perioperative complications (39% of 33 patients without pre-op transfusion versus 15% of 34 patients with pre-op transfusion, P-value = 0.023) in SCD patients (*Howard*). One observational study (717 patients) (*Koshy*) has demonstrated decreased sickle cell related post op complications in patients who had pre-op transfusion (12.9% vs. 4.8%, $P = 0.006$). However, several other observational studies demonstrated no difference. One large RCT (*Vichinsky*) did not show difference between simple transfusion (301 subjects, Hb of 10.6 g/dL, HbS of 59%) vs. exchange transfusion (303 subjects, Hb of 11 g/dL, HbS of 31%) in terms of sickle cell complication rate (35% vs. 31% overall and 10% ACS for both). In general, pre-op RBC transfusion should be used to bring Hb to 10 g/dL, but for patients with high baseline Hb such as in HbSC or HbSβ^+, partial or full RBC exchange may be used to avoid high viscosity, especially for high risk procedures like neurosurgery, prolonged anesthesia, and cardiac bypass procedures.

Prophylactic RBC exchange during pregnancy (Hydroxyurea is contradicted) had been reported to be associated with a lower risk of intrauterine growth restriction and can be performed safely, although careful fetal monitoring is recommended.

Rationale for therapeutic apheresis

The beneficial effects on blood viscosity, elasticity, and relaxation time, and reduction of adhesion molecule level like sVCAM-1 has been documented after RBC exchange. Chronic transfusion to maintain HbS <30% (some centers may use 50%) is indicated for prevention of primary and secondary stroke and to treat chronic debilitating pain. Manual exchange transfusion is labor intensive, prolonged and less efficient than RBC exchange. Both types of exchange transfusion used as initial or chronic transfusion therapy for patients with stroke are more effective in preventing subsequent stroke than simple transfusion. However, advantages of RBC exchange over simple transfusion have not been documented through RCTs. Long-term RBC exchange has the distinctive advantage of preventing or markedly reducing transfusional iron accumulation, but is associated with significantly (1.5 to 3 times) blood requirements than simple transfusion. 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 partial phenotypically-matched RBC.

Technical notes

Apheresis equipment calculates the replacement RBC volume to achieve the desired target HbS FCR and hematocrit levels. General guidelines to calculate replacement volume using COBE Spectra are: 1) End Hct at 30 ± 3% (≤33–36% to avoid hyperviscosity) and 2) HbS of 30% (or HbS + HbC of 30%, etc.). One can assume FCR at 25 - 40% in remotely transfused/never transfused patients. In recently transfused patients, FCR can be calculated by dividing the desired HbS level by pre-apheresis HbS level multiplied by 100. To maintain isovolemia, primed saline is not diverted and rinse back is omitted at the end of the run. In children, clinically unstable or severely anemic patients, 5% albumin may be used for priming**.** Modification of RBC exchange utilizing isovolemic hemodilution, which consists of RBC depletion with 0.9% NaCl replacement followed by standard RBC exchange, reduces replacement RBC volume and thus potentially donor exposure.

Volume treated: Volume necessary to achieve target HbS level
Replacement fluid: HbS negative leukoreduced RBCs and, if available, antigen-matched for at least C, E, and K.
Frequency: As needed to maintain target HbS level

Duration and discontinuation/number of procedures

Duration and number of RBC exchanges depend upon clinical indications, for example, one time for pre-op, variable times for chronic pain, and life-long for stroke prevention.

References [1271–1305]

*As of December 19, 2012 using PubMed and the MeSH search terms sickle cell disease, RBC exchange transfusion, and erythrocytapheresis for articles published in the English language. References of identified articles were searched for additional cases and trials.

STIFF-PERSON SYNDROME

Incidence: 0.1/100,000	**Procedure** TPE	**Recommendation** Grade 2C	**Category** III
# of reported patients*: <100			
RCT	**CT**	**CS**	**CR**
0	0	3 (12)	7 (7)

Description of the disease

Stiff-person syndrome is a rare chronic, but not usually progressive, disorder characterized by fluctuating muscle rigidity in the trunk and limbs as well as increased sensitivity to noise, touch and emotional distress which can result in muscle spasms. Co-contractions of agonist and antagonist muscles and continuous involuntary firing of motor units at rest occur. People with stiff-person syndrome typically have abnormal hunched over posture, and can be unable to walk or move. Stiff-person syndrome is more common in women than men and is often associated with autoimmune diseases including Graves' disease, Hashimoto's thyroiditis, pernicious anemia, and type I diabetes mellitus. Autoantibodies reactive to 65 kDa glutamic acid decarboxylase (GAD65, the enzyme responsible for the synthesis of GABA) in brain and pancreatic islet cells were found present in serum 90% of patients with stiff-person syndrome. These antibodies block GABA synthesis. Individuals may also have partial form or a rapidly progressive form known as progressive encephalomyelitis with rigidity and myoclonus (PERM). Seronegative individuals are more likely to have a coexisting cancer (25% vs. 4%), including breast, colon, small cell lung cancer, and Hodgkin's lymphoma. The paraneoplastic form of the syndrome is associated with autoantibodies to the 128 kDa synaptic protein amphiphysin.

Current management/treatment

Treatment is with a variety of medications including immune therapies, antianxiety medications, muscle relaxants, anticonvulsants and pain relievers. Diazepam, a benzodiazepine that diminishes continuous motor unit activity through inhibition of central catecholamine neurons and activation of GABAnergic neurons, is given 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 IVIG (2 g/kg per month in two consecutive daily doses of 1 g/kg) is effective in relieving symptoms of stiffness and spasticity, and in reducing the titer of anti-GAD65 antibodies. Rituximab did not prove effective.

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 plasma exchange 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.

Technical notes

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.

Volume treated: 1–1.5 TPV	**Frequency:** Every 1–3 days
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

A series of 4–5 plasma exchanges of 1–1.5 plasma volumes performed 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 [1306–1314]

*As of July 1, 2012 using PubMed and the MeSH search terms stiff-person syndrome and apheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

SUDDEN SENSORINEURAL HEARING LOSS

Incidence: 10–20/100,000	**Procedure**	**Recommendation**	**Category**
	LDL apheresis	Grade 2A	III
	Rheopheresis	Grade 2A	III
	TPE	Grade 2C	III

# of reported patients*: >300	**RCT**	**CT**	**CS**	**CR**
LDL apheresis	3 (360)	0	2 (224)	1 (1)
Rheopheresis	1(240)	0	2(31)	0
TPE	0	0	1(21)	1(1)

Description of the disease

Sudden sensorineural hearing loss (SSHL) is hearing loss of at least 30 dB in three sequential frequencies on standard pure tone audiogram occurring over < 3 days. It has an equal gender distribution and a wide age distribution with an average age of occurrence of 50–60 years. Simultaneous bilateral hearing loss occurs in 5% of cases. Hearing loss may be accompanied by tinnitus (80%), aural fullness (80%) and vertigo (30%). SSHL has a spontaneous recovery rate of 40–65%. The pathophysiology is uncertain with three proposed mechanisms: (1) viral infection of the cochlea or cochlear nerve, (2) autoimmunity toward inner ear antigens, and (3) vascular occlusion or decreased vascular flow in the terminal labyrinthine artery.

The terminal nature of the blood supply to the cochlea results in ischemia and cochlear injury when increased viscosity and/or abnormal vasomotor regulation occur. Risk factors for SSHL include hypercholesterolemia and hyperfibrinogenemia. Lowering of fibrinogen and/or cholesterol levels is associated with hearing recovery. In addition, elevated blood cholesterol levels lead to elevated cholesterol within the perilymph of the cochlea. The cochlear hair cell lateral walls are low in cholesterol. Elevated perilymph cholesterol increases lateral wall membrane cholesterol increasing membrane rigidity and decreasing hair cell function.

Current management/treatment

Treatment is focused on decreasing inflammation and improving blood flow. High-dose IV corticosteroids followed by an oral corticosteroid taper or intra ear steroid injection is used to treat possible inflammation. Pentoxifylline is given to improve red cell flexibility and reduce blood viscosity. IV dextran, hydroxyethyl starch, or glycerol are administered daily for 10 days to decrease whole blood viscosity.

Rationale for therapeutic apheresis

Elevated fibrinogen and LDL cholesterol have been identified as risk factors and decreasing these with medication has been associated with recovery of hearing. Acute reduction of these substances is possible with apheresis.

Three randomized controlled trials evaluated the use of the heparin-induced extracorporeal LDL apheresis (HELP) in treating SSHL. A trial of 27 patients (*Suckfull*) found greater hearing recovery at 24 h and 6 weeks with HELP but this was not statistically significant. A trial of 201 patients (*Suckfull*) found similar results, improved hearing which was not statistically different from standard therapy. The final trial (*Bianchin*) examined HELP as a standard therapy adjunct. Standard therapy plus HELP (72 patients) was compared to standard therapy (60 patients) in patients with elevated LDL cholesterol and/or fibrinogen. Statistically significant and clinically relevant hearing recovery measured by averaging audiometry results at 4 frequencies was seen in the standard treatment plus HELP group at 24 h (75% vs. 41%) and 10 days (76% vs. 45%). Finally, a case series of 217 patients (*Heigl*) who failed to responded to standard therapy examined HELP as salvage therapy. Improvement was seen in 61% with the time between onset of hearing loss and HELP treatment determining response. Response rate declined by 71% if treatment occurred more than two weeks after symptom onset.

A multicenter, randomized, controlled trial comparing rheopheresis (93 patients), corticosteroids (40 patients), and hemodilution (59 patients) found all three equally efficacious (*Mosges*). The rheopheresis group had a higher quality of life score on a standardized questionnaire. This was felt due to the limited course of therapy (1 to 2 treatments) compared to the 10 days of infusion for the other regimen. Those with higher plasma viscosity (>1.8 mPas) or higher plasma protein levels (>74 g/dL) had a higher rate of hearing recovery at 48 h compared to the other regimen. A case series of 25 patients who failed standard therapy (*Uygun-Kiehne*) found a 68% improvement (40% complete hearing recovery and 28% partial recovery) following two rheopheresis procedures.

A fibrinogen selective column was used in a prospective case series of 36 SSHL patients (*Ullrich*). Of the 36, 16 had spontaneous hearing recovery prior to treatment. Remaining patients recovered following daily procedures performed until a target fibrinogen of 80–100 mg/dL was achieved.

A single case report (*Alpa*) and a single case series (*Luetje*) using TPE in patients with SSHL have been published. In the case report, TPE resulted in hearing recovery in the ear not previously affected by SSHL. In the case series, 21 patients with SSHL due to presumed autoimmunity (testing for antibodies was not performed) were treated with TPE. Of 16 patients with >2 year follow-up, 50% demonstrated improved or stable hearing. The authors reported 4/16 patients required continued steroid therapy.

Technical notes

Patients with LDL cholesterol or fibrinogen elevations respond to apheresis treatment more rapidly and with greater improvement. Specific trigger levels have not, however, been suggested. Longer time between symptom onset and treatment is associated with poorer hearing recovery.

Volume treated: LDL apheresis: 3 L; rheopheresis: 1 TPV; TPE: 1 TPV
Frequency: LDL apheresis: 1–2; rheopheresis: 1–2; TPE: 3 every other day
Replacement fluid: LDL apheresis: NA; rheopheresis: NA; TPE: albumin

Duration and discontinuation/number of procedures

For HELP and rheopheresis, 1–2 procedures were performed on consecutive days, depending upon response as determined by standard audiometry. In the TPE case series, treatment was repeated if the patient's hearing deteriorated after initial improvement.

References [1315–1332]

*As of October 21, 2012 using PubMed and the MeSH search terms apheresis and hearing loss, sudden for articles published in the English language. References of the identified articles were searched for additional cases and trials.

SYSTEMIC LUPUS ERYTHEMATOSUS

Incidence: 15–50/100,000/yr	**Condition**	**Procedure**	**Recommendation**	**Category**
	Severe	TPE	Grade 2C	II
	Nephritis	TPE	Grade 1B	IV

# of reported patients*: >300				
	RCT	**CT**	**CS**	**CR**
Severe	1(20)	1(4)	14(128)	61(63)
Nephritis	4(78)	2(114)	6(160)	10(11)

Description of the disease

Systemic lupus erythematosus (SLE) is a chronic inflammatory disorder where circulating autoantibodies, immune complexes, and complement deposition leads to cell and tissue injury. The disease preferentially affects childbearing age females (ratio F:M 10:1). Ethnicity may affect disease severity, with African Americans presenting with more severe forms. Mortality of 70% at 10 years is typically due to infections and renal failure. Clinical symptoms may be nonspecific (e.g., fatigue, malaise, fever, anorexia, nausea, weight loss) and/or directly attributable to the involvement of one or more organ systems. The disease can affect any organ. Renal involvement in SLE (i.e., lupus nephritis) is associated with high mortality, but the extent and rate of progression is highly variable. Pathogenesis of SLE seems to be more complex than simple deposition of DNA-antiDNA complexes. Recent observations point towards 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. Recent studies also underscore potential role of T regs [CD4+CD25(high)FoxP3+], which are significantly decreased in the patients with SLE.

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, 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 antitumor necrosis factor therapy but controlled trials of these agents have not been performed. Belimumab, a fully human monoclonal antibody (B-lymphocyte stimulator (BlyS) inhibitor) was recently approved for treatment of SLE other than lupus nephritis or neuropsychiatric lupus (*Boyce*). In addition, HSC transplantation is now viewed as salvage therapy for intractable lupus by inducing very long-term immunologic remission (*Marmont*). One study reported 76% five-year survival. Patients with end-stage nephritis are treated with dialysis and renal transplantation.

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 to 2 or 0 to 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 (an increase in SLEDAI by >3), improvement (a reduction of SLEDAI by >3), persistently active disease (a change in SLEDAI $\pm \leq 3$) and remission (SLEDAI of 0).

Rationale for therapeutic apheresis

TPE was initially used to treat SLE under the assumption that removing pathogenic autoantibodies and immune complexes would control disease activity. However, this rationale has not translated into a clear clinical response. In the early 1980's 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 four liter exchanges within 2 weeks with expected autoantibody and immune complex reductions, showed no clinical improvement (*Wei*). More recently, the use of cyclosporine and TPE to control symptomatic disease in a prospective trial of 28 patients with flares resulted in quicker resolution of symptoms and decreased doses of cytotoxic drugs (*Bambauer*). Multiple well-documented case reports of beneficial effect of TPE in SLE associated TTP, DAH, MG, hyperviscosity, and cryoglobulinemia have been published. A 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 (*Neuwelt*). These results highlighted a potential benefit for refractory or critically ill patients. Addition of TPE to immunosuppressive therapy in SLE patients with DAH has been also reported.

In a small noncontrolled trial of patients ($n = 5$) undergoing TPE in the setting of severe SLE, it has been reported that during the course of TPE (4–6 days) the peripheral level of T regs cells significantly increased. The increased number of T regs was accompanied by a decrease in the disease activity as measured by SLEDAI. This observation could be due to the elimination of interferon alpha and lymphocytotoxic antibodies.

TPE in lupus nephritis is classified as Category IV insofar as a controlled trial of TPE plus prednisone and cyclophosphamide versus prednisone and cyclophosphamide in patients with severe lupus nephritis showed no benefit (*Lewis*). Smaller later trials have supported these findings. A recent randomized trial of severe lupus nephritis (*Loo*) suggested that adjunctive IA and TPE were equally effective in reducing SLEDAI scores. IA may be achieved with different high affinity columns.

Technical notes

Volume treated: 1–1.5 TPV	**Frequency:** Lupus cerebritis or SLE with DAH: daily or every other day;
Replacement fluid: Albumin, plasma	SLE other: 1−3 times per week

Duration and discontinuation/number of procedures

Typically a course of 3–6 TPE is sufficient to see response in the patients with lupus cerebritis or DAH. Prolonged treatments have been reported but its efficacy and rationale is questionable.

References [1333–1351]

*As of December 18, 2012 using PubMed and the MeSH search terms SLE, plasmapheresis, plasma exchange, apheresis and photopheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

THROMBOCYTOSIS

Incidence: ET: 1.5/100,000/yr; PV: 1.4/100,000/yr	**Condition**	**Procedure**	**Recommendation**	**Category**
Prevalence: ET, PV: 23/100,000	Symptomatic	Thrombocytapheresis	Grade 2C	II
# of reported patients*: 100–300	Prophylactic or secondary	Thrombocytapheresis	Grade 2C	III

	RCT	**CT**	**CS**	**CR**
Symptomatic	0	0	7(180)	24(29)
Prophylactic or secondary	0	0	2(39)	3(4)

ET = essential thrombocytopenia; PV = polycythemia vera

Description of the disease

Thrombocytosis, defined as a circulating platelet count $\geq$350–400 $\times$ 10^9/L, is more commonly caused by reaction to acute bleeding, hemolysis, infection, inflammation, asplenia, cancer or iron deficiency. The increased normal platelets do not predispose to thrombosis or bleeding because the platelets are normal. In contrast, the platelets in myeloproliferative diseases (MPDs), including essential thrombocythemia (ET), polycythemia vera (PV), CML, prefibrotic primary myelofibrosis (PMF) and refractory anemia with ring sideroblasts with marked thrombocytosis, are functionally abnormal and the thrombocytosis is associated with thrombohemorrhagic events.

ET is a clonal MPD characterized by autonomous overproduction of predominantly platelets. The *JAK2* gene point mutation (JAK2V617F) is found in roughly 40% of ET patients; absence of the gene mutation does not rule out ET. Bone marrow examination and *BCR-ABL* testing is needed to further distinguish other MPNs. Factors associated with poor survival, leukemic transformation and fibrotic progression, are age >60 years, anemia, white blood cell count >11 $\times$ 10^9/L and thrombosis history. Arterial or venous thromboembolic events, include microcirculatory thrombosis, cerebrovascular accidents, myocardial infarction, venous thromboembolism and first-trimester pregnancy loss, occur either spontaneously, or during situational hypercoagulability, such as with surgery or pregnancy. The cumulative rates of thromboembolism is 1.9–3% per patient per year in ET. The absolute platelet count and *in vitro* qualitative platelet function abnormalities are not predictive of thrombotic risk. ET can also lead to bleeding, which usually occurs in mucocutaneous sites (rarely GI) and affects 2–37% of patients. Acquired defects in platelet aggregation are thought to be the major mechanisms responsible for the bleeding risk. However, the degree of platelet dysfunction (as measured by in vitro adhesion and aggregation assays) or the number of circulating platelets (when the count is >1,500 $\times$ 10^9/L) does not correlate with bleeding manifestations. Studies support a correlation between bleeding and platelet counts outside of the normal range (above or below), as well as extreme elevations platelet count is >1,500 $\times$ 10^9/L that is associated with acquired von Willebrand syndrome (AVWS). This can be measured by collagen binding activity (CBA), ristocetin cofactor activity, and loss of large VWF multimers. The risk of hemorrhage also appears to be increased when the white blood cell count is elevated. Splenectomy performed for palliation of pain or cytopenias in late stage MPDs, can be associated with extreme "rebound" thrombocytosis (i.e., >1000 $\times$ 10^9/L) in 5% of cases and postoperative thrombosis (10%) and bleeding (14%); however, the platelet count does not predict thrombohemorrhagic complications.

Current management/treatment

ET (as defined by WHO) has an estimated 15-year survival of 80%. Low-dose aspirin is indicated for thromboprophylaxis in low risk patients and is also useful in curtailing vasomotor symptoms such as headache, tinnitus, ocular disturbances and erythromelalgia. Low dose aspirin is also indicated in those with extreme thrombocytosis if the ristocetin cofactor activity is $\geq$30% (due to excess bleeding risk if <30%). In high risk patients, platelet-normalizing therapy with hydroxyurea, or interferon-α or busulfan when resistant to hydroxyurea, is indicated. A study of ET patients with extreme thrombocytosis found that the reduced VWF:CBA normalized after cytoreduction, suggesting that the platelet dysfunction was at least partially attributable to the binding and clearance of VWF by the excess platelets. The platelet count should be normalized before surgery, particularly splenectomy surgery, to minimize complications and avoid rebound thrombocytosis. Alternative platelet-lowering agents include anagrelide and interferon-α, which is the treatment of choice during pregnancy. Venous thromboembolic complications are treated acutely with unfractionated or low-molecular-weight heparin followed by therapeutic warfarin for 3–6 months. Arterial events are treated acutely with an antiplatelet agent or, less commonly, heparin. Anticoagulation or antiplatelet agents and cytoreductive therapy significantly lower the risk of recurrent thromboembolism. Secondary prevention also includes warfarin or an antiplatelet agent. Patients with extreme thrombocytosis and hemorrhage should be treated to lower the platelet count with medical therapy or thrombocytapheresis.

Rationale for therapeutic apheresis

Thrombocytapheresis has been utilized to prevent recurrent or treat acute thromboembolism or hemorrhage in selected patients with an MPN and uncontrolled thrombocytosis. Case reports describe rapid improvement of severe microvascular ischemic complications that are unresponsive to antiplatelet agents. Thrombocytapheresis has also been used to treat extreme rebound thrombocytosis after splenectomy and during pregnancy to prevent recurrent fetal loss in high-risk patients; although it is not indicated or beneficial for standard-risk pregnant women with PV or ET. Although the therapeutic mechanisms are not well defined, rapid cytoreduction is believed to ameliorate prothrombotic factors associated with the dysfunctional platelets. Restoring a normal platelet count corrects the short plasma half-life of large VWF multimers with ET; and this may be important for patients with AVWS and >1,500 $\times$ 10^9/L platelets. Pre- and postprocedure platelet counts should be closely followed to gauge the effectiveness of platelet removal and to guide subsequent treatments. Elective thrombocytapheresis should also be considered for cytoreduction of patients at increased risk of major hemorrhage when hydroxyurea is contraindicated, such as in pregnancy or in situations when the onset of action of hydroxyurea cytoreduction is too slow, such as the requirement for emergent surgery. Platelet-lowering agents must be given to prevent rapid reaccumulation of circulating platelets whenever possible. Although anecdotal case reports have described a potential benefit of thrombocytapheresis with secondary thrombocytosis, the rationale is undefined and efficacy unproven.

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 1:6–12; heparin should be avoided to prevent ex vivo platelet clumping. Methods of thrombocytapheresis typically differ from donor plateletapheresis, thus manufacturer's recommendations as well as published reports should be carefully considered prior to initiation of the procedure.

Volume treated: 1.5–2 TBV
Replacement fluid: Saline
Frequency: Daily or as indicated to reach/maintain goal

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. The goal for prophylaxis of high-risk patients who are pregnant, undergoing surgery or postsplenectomy 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 $\times$ 10^9/L or less may be sufficient.

References [929, 1124–1130, 1132, 1352–1371]

*As of October 19, 2012 using PubMed and the MeSH search terms thrombocytosis, essential thrombocythemia, polycythemia vera, plateletapheresis, thrombocytapheresis, apheresis, myeloproliferative disorder, myeloproliferative neoplasm for reports published in the English language. References of the identified articles were searched for additional cases and trials.

THROMBOTIC MICROANGIOPATHY, DRUG-ASSOCIATED

Incidence: Clopidogrel/Ticlopidine: .001% to .0625%; Cyclosporine / Tacrolimus: rare; Gemcitabine: .015% to 1.4%; Mitomycin 2–15%; Quinine: rare	**Condition**	**Procedure**	**Recommendation**	**Category**
	Ticlopidine	TPE	Grade 2B	I
	Clopidogrel	TPE	Grade 1B	III
	Cyclosporine/ tacrolimus	TPE	Grade 2C	III
	Gemcitabine	TPE	Grade 2C	IV
	Quinine	TPE	Grade 2C	IV

# of reported patients*: >300

	RCT	**CT**	**CS**	**CR**
Ticlopidine/Clopidogrel	0	0	4(152)	5(5)
Cyclosporine/Tacrolimus[+]	0	0	6(90)	7(7)
Gemcitabine	0	0	3(39)	9(11)
Bevacizumab	0	0	1 (6)	2 (2)
Quinine	0	0	3(32)	8(8)

[+]Evaluated in aggregate since these are frequently prescribed on alternating or tandem schedules.

Description of the disease

Thrombotic microangiopathy (TMA) refers to the histopathologic findings of arteriolar microthrombi with associated intimal swelling and fibrinoid necrosis of the vessel wall. A variety of drugs have been associated with platelet activation and intravascular microthrombi either confirmed by biopsy or correlated with the clinical findings of microangiopathic hemolytic anemia (MAHA) with schistocytes and thrombocytopenia. The presence of renal dysfunction, mental status changes and fever are variable depending on the associated drug. Severe deficiency (<10%) of ADAMTS13 and inhibitors to its activity have been documented in ticlopidine associated TMA. It has not been associated with clopidogrel-TMA suggesting there may be distinct mechanisms for TMA for these two related thienopyridine drugs. Most clopidogrel cases have mild hematologic and marked kidney involvement. In cyclosporine/tacrolimus associated TMA reported patients frequently do not have systemic manifestations. Cancer patients may develop TMA from (1) chemotherapy [mitomycin, cisplatin, bleomycin, 5-FU, Gemcitabine. FDA warns of risk with mitomycin and gemcitabine], and (2) targeted cancer agents [immunotoxins, monoclonal Ab, tyrosine kinase inhibitors]. TMA has also been associated with malignancy and HSC transplantation. In quinine-associated TMA, quinine-dependent antibodies directed at platelet glycoproteins as well as granulocytes, lymphocytes and endothelial cells have been documented.

Current management/treatment

Initial management of drug-associated TMA characteristically involves immediate discontinuation of the suspected drug or in some situations, reduction of dose when discontinuation is not a medical option. Supportive care and other specific interventions in addition to TPE reported for specific drugs include: Gemcitabine- dialysis, antihypertensives, corticosteroids; Cyclosporine/ Tacrolimus- change to different immunosuppressive drug; and Quinine- corticosteroids, antiplatelet agents. Bevacizumab discontinue drug, substitute steroids, cyclophosphamide, or other agents.

Rationale for therapeutic apheresis

The use of TPE for TMA is based on extrapolation of its effectiveness for idiopathic TTP. When measured, plasma ADAMTS13 levels have not demonstrated severe deficiency or inhibitors for many pharmaceuticals associated with TMA; with ticlopidine, however, activity is severely diminished at the time of TMA onset, with inhibitors. Not all patients with drug-associated TMA have hematologic manifestations. Alternative mechanisms proposed include autoimmunity, drug-dependent antibodies, and endothelial toxicity. Therefore, a therapeutic rationale for TPE is difficult to define, a fact that likely reflects the reported heterogeneous clinical results. In addition to pathogenic distinctions from idiopathic TTP, there may be confounding variables including the presence and progression of pre-existing medical conditions such as malignancy, renal failure, or hypertension. When patients present with MAHA and thrombocytopenia with other clinical and laboratory data consistent with TTP, TPE has been variably applied for management of drug-associated TMA. However, the mechanism of potential benefit is unknown and could include removal of plasma protein bound drug or metabolites. When TPE is considered for drug-associated TMA, potential benefits should be evaluated in conjunction with known risks of TPE, receipt of blood products, and vascular access. Specific drug information:

Ticlopidine: Most common drug associated with TMA in FDA safety databases. Ticlopidine used less due to agranulocytosis. Patients presenting 2 or more weeks after initial exposure had improved survival (84% vs. 38%, $P < 0.05$) with TPE; when presenting <2 weeks after drug initiated, survival with TPE or without TPE was similar (77% vs. 78%). The presence of severely deficient ADAMTS13 activity (<10%) with autoantibodies, similar to idiopathic TTP, may relate to the overall response of these patients to TPE.

Clopidogrel: Patients present within 2 weeks of starting therapy and lack deficient ADAMTS13 activity or inhibitors. (*Zakarija*) Only 50% of patients have been reported to respond to TPE. Clopidogrel cases may require up to 30 TPE before clinical improvement.

Cyclosporine/Tacrolimus: Response to TPE has been unpredictable even with extended duration of TPE. In one case report with documented inhibitor to ADAMTS13 and depressed activity (17%), TPE was associated with improvement.

Gemcitabine: Nucleoside analog approved for advanced malignancies. Incidence of atypical HUS is 1–2%. ADAMTS13 levels are typically normal. Literature review reported that of 26 patients not treated with TPE, 56% recovered from TMA; of 18 patients treated with TPE, 30% recovered. However, group receiving TPE appeared to be more severely ill and more likely to have received dialysis. Rituximab may be considered if TPE is not rapidly effective.

Bevacizumab: Addition of anti-VEGF monoclonal protein to chemotherapy regimens improved survival rates for colon, lung, and breast cancer. Used as single agent for renal cell cancer and intraocularly for choroidal neovascularization. TMA results from local reduction of VEGF within the kidney. Not associated with low ADAMTS13. One report (*Eremina*) described six treated cancer patients who developed TMA. One patient received five TPE, and kidney function stabilized. A case of TMA due to intravitreal ranizumab for macular degeneration noted (*Pelle*).

Quinine: May present clinically with MAHA and thrombocytopenia; however, the role of TPE is questionable since antibodies are directed to other constituents and not ADAMTS13. (*Park*) In one controlled case series comparing quinine-TMA to nonquinine TTP in TPE treated patients, mortality was 21% vs. 41%, respectively, and development of chronic renal failure was 57% vs. 16%. In uncontrolled case-series, mortality was 0% with TPE treated patients not lost to follow-up.

Technical notes

The specific TPE replacement fluid strategy and frequency are not described in the majority of published case reports. The pattern of response of platelet count, hematologic and laboratory parameters, and clinical signs may be variable and incomplete compared to patients undergoing TPE for idiopathic TTP. Otherwise, similar procedural considerations apply as with TPE for TTP.

Volume treated: 1–1.5 TPV **Frequency:** Daily or every other day
Replacement fluid: Plasma, plasma cryoprecipitate removed

Duration and discontinuation/number of procedures

TPE for drug-associated TMA is usually performed daily until recovery of hematologic parameters and then either discontinued or tapered, similar to treatment for idiopathic TTP. The therapeutic endpoint may be difficult to determine or attain because of confounding morbidity from underlying disease or other factors not yet recognized. The durability of response and frequency of relapse are undefined. Re-exposure to the associated drug should be avoided.

References [1372–1429]

*As of February 2012 using PubMed and the MeSH search terms thrombotic microangiopathy or HUS or TTP and plasmapheresis or plasma exchange and the respective drug: gemcitabine, quinine, cyclosporine, tacrolimus, ticlopidine, clopidogrel, thienopyridine for reports published in the English language. References of the identified articles were searched for additional cases and trials.

THROMBOTIC MICROANGIOPATHY, HEMATOPOIETIC STEM CELL TRANSPLANT ASSOCIATED

Incidence: 1-year cumulative 13% (non-myeloablative) versus 15% (high-dose); **Prevalence**:10–25%	**Condition**	**Procedure**	**Recommendation**	**Category**
	Refractory	TPE	Grade 2C	III

# of reported patients*: >300

RCT	**CT**	**CS**	**CR**
0	0	23(345)	6(6)

Description of the disease

TMA refers to the histopathological appearance of arteriolar microthrombi with associated intimal swelling and fibrinoid necrosis of the vessel wall. A variety of conditions and drugs can activate platelets causing their intravascular deposition as microthrombi, resulting in the clinicopathologic hallmarks of TMA: MAHA and thrombocytopenia. TMA following allogeneic HSC transplantation (also called transplant associated [TA]-TMA) appears to be primarily triggered by mechanisms of endothelial cell injury, including high-dose conditioning chemotherapy, irradiation, GVHD, mTOR and calcineurin inhibitor drugs (used to prevent and treat GVHD) and infections. Damaged and apoptotic endothelial cells generate microparticles, release of VWF and induce platelet adhesion/aggregation and a procoagulant state. In contrast to idiopathic TTP, the plasma ADAMTS13 protease level is not severely deficient nor is ADAMTS13 inhibitor activity detectable. The incidence of TA-TMA varies based on the diagnostic criteria and transplant-associated risk factors. Incidence rates in older studies ranged from 0.5%–63.6%; however, the rates in more recent studies range from 3%–15%. A recent review (*Willems*) reported 1-year cumulative incidence of 13% in nonmyeloablative setting versus 15% in the high-dose setting. Most large, retrospective studies report a prevalence of 10–25% (*Laskin*). Risk factors associated with TA-TMA include high dose conditioning regimens, acute GVHD, female sex, older age, active infections, unrelated donor transplants and the combination of mTOR and calcineurin inhibitor drugs. Kidneys are the major target organs of TA-TMA. Renal function test elevation is common and renal failure is a poor prognostic feature. Diagnostic criteria require MAHA (with high LDH or low haptoglobin) with or without unexplained thrombocytopenia, renal and/or neurologic dysfunction. Because MAHA can be due to other causes and drugs, the published criteria for TA-TMA diagnosis are relatively insensitive. TA-TMA can occur within the first few weeks following transplant or as a late complication (up to 8 months). TA-TMA carries a poor prognosis. Mortality rates range from 44–90%, including those patients who respond to interventions, due to renal failure, cardiac or brain ischemia, bleeding and complications of concurrent GVHD and/or infections.

Current management/treatment

Initial management of TA-TMA involves reduction or discontinuation of mTOR and calcineurin inhibitor drugs (especially if used in combination) along with aggressive treatment of underlying GVHD and infections. No randomized clinical trials have addressed the efficacy of TPE for TA-TMA. Case series have reported overall response rates with TPE (usually after drug withdrawal) ranging from 0–72%, but with frequent partial responses, relapses and up to 15% procedural adverse events. One recent study of 63 patients observed TPE responses only among those who also responded to treatment of GVHD and/or infections, suggesting that plasma exchange alone does not reverse the TMA pathophysiology. A systematic review by George et. al. of published cases up to 2004 noted an 82% mortality rate among 176 patients with TA-TMA who underwent TPE compared to 50% mortality among 101 patients not treated with TPE. Similarly high cumulative mortality rates were cited by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Toxicity Committee in a 2005 consensus statement that recommended TPE not be considered as a standard of care for TA-TMA. Because some patients appear to respond to TPE, a trial of plasma exchange could be considered as salvage therapy for selected patients with persistent/progressive TA-TMA despite resolution of infections and GVHD. Other salvage treatment options, based on anecdotal reports, might include daclizumab, defibrotide and rituximab.

Rationale for therapeutic apheresis

The use of TPE for TA-TMA is based on extrapolation of its effectiveness for idiopathic TTP. However, numerous studies have confirmed that plasma ADAMTS13 protease levels are not severely deficient nor are ADAMTS13 inhibitors detectable in patients with TA-TMA. Therefore, a therapeutic rationale is undefined and consistent with the uncertain clinical efficacy.

Technical notes

TPE for patients with TA-TMA is often complicated by thrombocytopenia, anemia and the comorbidities related to GVHD and infections, including bleeding and hypotension. Therefore, the pattern of platelet and LDH responses may be variable and incomplete compared to patients undergoing TPE for idiopathic TTP. Otherwise, similar procedural considerations apply as with TPE for TTP.

Volume treated: 1–1.5 TPV	**Frequency:** Daily, or as indicated for chronic management
Replacement fluid: Plasma, plasma cryoprecipitate removed	

Duration and discontinuation/number of procedures

TPE for TA-TMA is usually performed daily until a response and then either discontinued or tapered off, similar to treatment for idiopathic TTP. The therapeutic endpoint may be difficult to determine because the platelet count and LDH levels could be affected by incomplete engraftment and post-transplant complications. Because MAHA may be caused by other disorders and drugs post-transplant, isolated persistence of schistocytes on the peripheral blood smear, without other clinical manifestations of TMA, may not preclude discontinuation of treatment.

References [1430–1448]

*As of October 15, 2012 using PubMed and the MeSH search terms thrombotic microangiopathy, stem cell transplantation, transplantation-associated TMA, transplant-associated microangiopathy for reports published in the English language. References of the identified articles were searched for additional cases and trials.

THROMBOTIC THROMBOCYTOPENIC PURPURA

Incidence: 0.37/100,000/year (US)	**Procedure** TPE	**Recommendation** Grade 1A	**Category** I
# of reported patients*: >300			
RCT	**CT**	**CS**	**CR**
7 (301)	2 (133)	26 (980)	46 (83)

Description of the disease

TTP is a systemic thrombotic illness affecting mostly small vessels. When initially described, TTP was defined by a pentad of clinical findings: thrombocytopenia, MAHA (fragmented red cells on blood smear and elevated LDH), mental status changes, renal failure and fever. In current practice, however, the clinical findings of unexplained thrombocytopenia and MAHA are sufficient to diagnose TTP. Treatment is usually initiated in an "urgent and empirical" manner, that is, usually within 4–8 h of presentation, after other causes of systemic thrombotic microangiopathy (TMA) such as DIC, severe malignant hypertension, HUS and post-transplant TMA have been considered unlikely and a working clinical diagnosis of TTP is made. More recently TTP was shown to be associated with a severe (<5%) deficiency of plasma ADAMTS13 (***A d**isintegrin **a**nd **m**etalloproteinase with a **t**hrombo**s**pondin type 1 motif, member 13)* enzyme activity, which is responsible for maintaining normal distribution of VWF multimers by cleaving ultra large multimers released from the endothelium. In seven earlier studies, severe deficiency of ADAMTS13 was documented in 100% of patients with idiopathic TTP. By comparison, severe deficiency was identified in 37–83% of patients in five other studies, highlighting the variable reliability of this parameter as a diagnostic criterion. The presence of an identified autoantibody in the majority of patients with idiopathic acquired TTP and severe ADAMTS13 deficiency suggests an acquired autoimmune disorder. IgG4 is the most common anti-ADAMTS13 IgG subclass and appears to be related to recurrence of the disease. Congenital TTP is associated with somatic mutations resulting in severely deficient ADAMTS13 function. ADAMTS13 deficiency appears to be an important proximal step in the pathophysiology of congenital and idiopathic acquired TTP, however, the role of laboratory assays that measure protease activity and anti-ADAMTS13 antibody level in medical decision-making in TTP is still evolving. Similarly, diagnostic criteria to differentiate TTP from HUS (characterized by TMA, thrombocytopenia, and renal failure) are still not definitive. **At this time TTP remains a clinical diagnosis**. The course may be long with relapses. Because TTP is potentially fatal if left untreated, there should be a low threshold to treat presumed TTP. Pregnancy, connective tissue disease, medications, infection, cancer, and transplantation are all associated with TTP, HUS and TMA syndromes (see fact sheets on hemolytic uremic syndrome, atypical; hemolytic uremic syndrome, infection associated; TMA drug-associated and TMA HSCT-associated).

Current management/treatment

TPE has decreased the overall mortality of idiopathic TTP from uniformly fatal to <10%. TPE should be initiated emergently once TTP is recognized. If TPE is not immediately available, plasma infusions may be given until TPE can be initiated. Both plasma and cryoprecipitate poor plasma (less VWF) 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/day; however, no definitive trials to prove their efficacy have been performed. Rituximab is now often used to treat refractory or relapsing TTP and recent studies have described incorporation of rituximab as an adjunctive agent with initial TPE. Since rituximab immediately binds to CD20-bearing lymphocytes, an interval of 18–24 h between its infusion and TPE has been used in practice. Other adjuncts include cyclosporine, azathioprine, vincristine and other immunosuppressive agents. Splenectomy was used in the past. 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 without a clinical indication such as intracranial hemorrhage. 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 ADAMTS13) or plasma derived VWF concentrates (used to treat von Willebrand disease) have been used.

Rationale for therapeutic apheresis

TPE with plasma replacement has significantly improved patients' clinical outcomes. No other intervention has had as significant impact on the treatment of acquired idiopathic TTP. One hypothesis is that TPE removes the anti-ADAMTS13 autoantibody, while restoring ADAMTS 13 protease activity. However, the clinical course does not always correlate with plasma ADAMTS13 activity or ADAMTS13 inhibitor and/or levels.

Technical notes

Transfusion of RBC, when medically necessary, may be given emergently during TPE. Clinical response with clearing of mental status usually precedes recovery of platelet count and normalization of LDH. 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 cryoprecipitate poor plasma as replacement. In patients with severe allergic reactions to plasma proteins or limited supply of ABO compatible plasma, albumin may be substituted for the initial portion (up to 50%) of replacement. Albumin alone, however, has never shown efficacy.

Volume treated: 1–1.5 TPV	**Frequency:** Daily
Replacement fluid: Plasma, cryoprecipitate poor plasma	

Duration and discontinuation/number of procedures:

TPE is generally performed daily until the platelet count is above 150×10^9/L, and LDH is near normal for 2 to 3 consecutive days. The role of tapering TPE over longer duration has not been studied prospectively but is used frequently. Persistence of schistocytes alone on peripheral blood smear, in the absence of other clinical features of TTP, does not preclude discontinuation of treatment.

References [1449–1470]

*As of January 11, 2013 using PubMed and the MeSH search terms TTP, plasma exchange, plasmapheresis and rituximab reports published in the English language. References of the identified articles were searched for additional cases and trials.

THYROID STORM

Incidence: Rare	**Procedure** TPE	**Recommendation** Grade 2C	**Category** III
# of reported patients*: <100			
RCT	**CT**	**CS**	**CR**
0	0	4 (23)	20 (25)

Description of the disease

Thyroid storm or accelerated hyperthyroidism is an extreme manifestation of thyrotoxicosis. This uncommon but serious complication occurs mostly in Graves' disease and less often in the setting of toxic multinodular goiter. Symptoms are usually precipitated by infection, trauma, surgical emergencies, or operations and, less commonly, by radiation thyroiditis, diabetic ketoacidosis, toxemia of pregnancy, or parturition. It is postulated that cytokine release and immunologic responses caused by these conditions trigger thyroid storm. Amiodarone-induced thyroid storm is more prevalent in iodine-deficient geographic areas. The crises are usually sudden in patients with preexisting hyperthyroidism that has been treated partially or not at all. Burch and Wartofsky created a scoring system to help standardize the diagnosis of thyroid storm using the following parameters: body temperature, CNS involvement, GI-hepatic dysfunction, heart rate, and presence or absence of congestive heart failure and/or atrial fibrillation. The severity of the symptoms correlates with the number of points, for a possible total of 140. A score of 25–44 is considered high risk for an imminent storm, and a score $\geq$45 is diagnostic of thyroid storm. Overall, the clinical picture is one of severe hypermetabolism. Fever is almost invariably present and may be >104 F with profuse sweating. Marked tachycardia and arrhythmias may be accompanied by pulmonary edema or congestive heart failure. Tremulousness and restlessness are present; delirium or frank psychosis may supervene. Nausea, vomiting, and abdominal pain may occur early in the course. As the disorder progresses, apathy, stupor, and coma follow, and hypotension can develop. If unrecognized, the condition may be fatal. However, mortality is 10–30% even with treatment. This clinical picture in a patient with a history of preexisting thyrotoxicosis or with goiter or exophthalmos, or both, is sufficient to establish the diagnosis, and emergency treatment should not await laboratory confirmation. The serum thyroid hormone levels in thyroid storm are not necessarily higher than during severe uncomplicated thyrotoxicosis. However, the patient can no longer adapt to the metabolic stress. Thus, there is no serum T_3 or T_4 concentration that discriminates between severe thyrotoxicosis and thyroid storm. It is prudent to consider the latter and treat the patient aggressively rather than wait until the patient meets all the objective criteria for thyroid storm.

Current management/treatment

Patients with thyroid storm must be monitored in the intensive care unit during the initial phases of treatment. Their management includes medications which stop the synthesis (propylthiouracil or methimazole), release (iodine) and peripheral effects of the thyroid hormones (beta-blockers such as propranolol) as well as the high fever (acetaminophen) or hypotension (hydrocortisone). If a precipitating event is present, it should also be treated concurrently. The order of treatment is very important. Propylthiouracil (preferred drug) should be started before iodine in order to prevent stimulation of more thyroid hormone production which could happen if iodine were given initially. Depending on the clinical status of the patient, the two agents may be administered as close as 30–60 min apart. Large doses of an antithyroid agent (300–400 mg of propylthiouracil every 4–6 h) are given by mouth, by stomach tube, or, if necessary, per rectum. Propylthiouracil is preferable to methimazole because it has the additional action of inhibiting the peripheral generation of T_3 from T_4 in peripheral tissues and in the thyroid itself. Controlling the cardiovascular manifestations of thyroid storm is a vital part of management. Sinus tachycardia, atrial fibrillation, and congestive heart failure are common findings which may occur alone or in combination. Relatively large doses (greater than 160 mg daily) of propranolol are usually required because of the faster metabolism of the drug, and possibly because of an increased number of cardiac beta-adrenergic receptors.

Rationale for therapeutic apheresis

Several alternative agents are reserved for patients with thyroid storm when the first-line therapies outlined above fail or cannot be used due to toxicity. TPE is among them, although a variety of drugs should be tried first. TPE becomes an option when clinical deterioration occurs despite the use of first- and/or second-line therapies. Since a portion of T_3 and T_4 is firmly bound to plasma proteins, TPE should, in theory, efficiently reduce their circulating pool. While the literature contains conflicting reports, most patients had a decrease in the hormone concentrations. In one report, TPE increased the elimination of total T_4 approximately 30-fold compared with standard medical treatment. This effect was dependent on the serum level of T_4, 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. TPE in this condition is particularly indicated for patients who have no underlying thyroid disease and develop a drug-induced destructive thyroiditis. The therapeutic benefit of TPE can also be as a result from the removal of the potential substances from the thyroid storm such as autoantibodies (Graves' disease), catecholamines (released by the sympathetic system) and cytokines. In rare cases, TPE is used to render the patient euthyroid prior to thyroidectomy.

Technical notes

Plasma as replacement fluid has the advantage of increasing the concentration of thyroglobulin to bind free thyroid hormone.

Volume treated: 1–1.5 TPV	**Frequency:** Daily or every 2–3 days
Replacement fluid: Plasma, albumin	

Duration and discontinuation/number of procedures

TPE should be continued until clinical improvement is noted.

Referenes [1471–1487]

*As of July 5, 2012 using PubMed and journal published in English language using the search terms thyrotoxicosis, thyroid storm, hyperthyroidism, TPE, and plasmapheresis. References of the identified articles were searched for additional cases and trials.

TOXIC EPIDERMAL NECROLYSIS

Incidence: 1–7/1,000,000/yr	**Condition** Refractory	**Procedure** TPE	**Recommendation** Grade 2B	**Category** III
# of reported patients*: <100				
RCT	**CT**	**CS**		**CR**
0	0	11 (83)		2 (2)

Description of the disease

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), also called Lyell syndrome, are severe idiosyncratic reactions with medications being the most common trigger. They are characterized by mucocutaneous lesions leading to necrosis and sloughing of the epidermis. These entities are not to be confused with erythema multiforme which is characterized by distinctive target-like lesions on the skin and most often associated with infection (particularly herpes simplex). Classification of SJS and TEN is determined mainly by severity and percentage of body surface involved. SJS is the less severe condition, in which skin sloughing is limited to <10% of body surface area (BSA) while mucous membranes are affected in >90% of patients. TEN involves sloughing of >30% BSA with nearly 100% involvement of mucous membranes. In SJS/TEN overlap syndrome, patients have BSA involvement of >10% but <30%. Exposure to the inciting drug commonly precedes the onset of symptoms by 1–3 weeks in medication-related cases. Upon re-exposure, symptoms may recur in as little as 48 h. Typically there is a prodrome of fever and flu-like symptoms. In the early stages of the disease, skin pain may be prominent and out of proportion to clinical findings. Skin lesion distribution is symmetrical, and starts on the face and chest before spreading to other areas. Vesicles and bullae form and the skin begins to slough within days. Sloughing progresses rapidly for a few days and then usually stabilizes. Fulminant cases of TEN highly resistant to therapy have been described. Anemia and lymphopenia are common in TEN. Neutropenia is noted in approximately one-third of TEN patients, and is correlated with a poor prognosis. Overt hepatitis may be seen in a minority of patients. SJS/TEN causes significant morbidity and full recovery typically requires 2–3 weeks. Skin biopsy shows perivascular mononuclear inflammatory infiltrate comprised primarily of T-lymphocytes in the early stages. In severe presentations, full thickness epidermal detachment with splitting above the basement membrane, with minimal inflammatory infiltrate is seen. Mortality in SJS is 1–3%, while mortality ranges vary significantly for TEN with some case series documenting mortality as high as 50%.

Current management/treatment

For medication-induced SJS/TEN, the causative medication is immediately withdrawn. Delayed removal of the causative drug and drugs with long half-lives are associated with worse prognosis. A prognostic scoring system (SCORTEN) based upon easily measured clinical and laboratory variables has been validated for use on days one and three of hospitalization for TEN. Supportive care is the mainstay of treatment and includes care of skin lesions, fluid and electrolyte management, nutritional support, eye care, temperature management, appropriate analgesia, and treatment of infections. Fluid and electrolyte losses may occur due to the extensive mucocutaneous lesions. SJS/TEN patients are at high risk for infection, and sepsis is a major cause of death in these patients. Aggressive culturing and sterile precautions are important in minimizing this risk. Beyond supportive care, there are no universally accepted therapies for this disease. Glucocorticoids, cyclosporine and IVIG have been used in the management but there are no controlled trials performed that can help assess efficacy of these agents in TEN, and their utility is still debated in this setting.

Rationale for therapeutic apheresis

The pathogenesis of SJS/TEN is incompletely understood. A number of risk factors including genetic (certain HLA types; slow acetylators), viral infections, and immunologic diseases have been proposed. Proposed mechanisms implicate granulysin (a protein secreted by cytotoxic T and NK cells), fas/fas-ligand mediated keratinocyte apoptosis, perforin, reactive-oxygen species and TNF-alpha in mediating keratinocyte cell death. Removal of a toxin, such as a drug/drug metabolite, or other mediators of keratinocyte cytotoxicity (discussed above) are proposed as rationale for TPE treatment. Numerous case series have utilized TPE in the setting of severe cases of TEN refractory to standard treatment. Protocols of TPE use have been varied. All but one case series have suggested that TPE has been efficacious. Outcomes monitored have included mortality, sepsis, need for mechanical ventilation, length of hospital stay, and time to re-epithelialization. Given the retrospective nature of these studies, heterogeneity in patient condition at the time of initiation of TPE, the number of TPE treatments utilized, different concurrent medications that these patients were on, and varied disease severity, a rigorous evaluation of TPE efficacy in TEN is challenging. TPE has not been used in patients with SJS.

Technical notes

While most reports have utilized TPE to treat refractory TEN, some groups from Japan have also used DFPP, which is not available in US.

Volume treated: 1–1.5 PV	**Frequency:** Daily or every other day
Replacement fluid: Plasma, albumin	

Duration and discontinuation/number of procedures

The number of TPE treatments vary considerably from 1 to >5 procedures and discontinuation has been guided by clinical improvement (most frequently skin healing and re-epithelialization)

References [1488–1506]

*As of October 10, 2012 using PubMed and the MeSH search terms Steven-Johnson syndrome, toxic epidermal necrolysis, Lyell syndrome, plasma exchange, and plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

VOLTAGE GATED POTASSIUM CHANNEL ANTIBODY RELATED DISEASES

Incidence: Rare	**Procedure** TPE	**Recommendation** Grade 1C	**Category** II
# of reported patients*: <100			
RCT	**CT**	**CS**	**CR**
0	0	5 (28)	22 (24)

Description of the disease

Voltage gated potassium channel (VGKC) antibody related diseases is also known as limbic encephalitis, neuromyotonia, and Morvan's syndrome. VGKCs belong to a family of voltage-gated shaker-like potassium channels. These membrane proteins are made up of tetramers (usually hetero-tetramers of different subtypes). VGKCs are expressed by a wide range of cells, but are most important in the control of membrane excitability in the nervous system. There are several subtypes of the VGKCs. Those binding dendrotoxin (i.e., Kv1.1, Kv1.2, and Kv1.6) are most likely to be targets for autoantibodies.

The presence of VGKC autoantibodies, which were initially considered paraneoplastic, was reported in a wide variety of acute and subacute neurological presentations including cognitive impairment, seizures, dysautonomia, myoclonus, dyssomnia, peripheral nerve dysfunction, extrapyramidal dysfunction, brainstem/cranial nerve dysfunction and startle syndrome as well as in some patients with neoplastic conditions (carcinomas, adenomas, thymoma and hematologic malignancies). The latter is a minority of patients with VGKC autoantibodies. Three neurological conditions have been strongly associated with the presence of VGKCs autoantibodies and include limbic encephalitis (LE), acquired neuromyotonia (NMT) and Morvan's syndrome (MVS). LE is characterized by impairment of recent memory, hallucinations, abnormal behavior, seizures and sleep disturbances. Neuromyotonia is defined by spontaneous firing of peripheral neurons leading to stiffness, difficulty in muscle relaxation, and fasciculation. In both conditions, males are predominantly affected. The initial presentation tend to occur in the 5th decade for NMT and 6th/7th decade of life in LE. Finally, MVS presents with autonomic dysfunction in addition to the symptoms seen in LE and NMT. The long-term prognosis varies from poor to spontaneous remission (seen in a very few cases).

Current management/treatment

The wide spectrum of clinical presentations makes differential diagnosis complex and many patients suffer from the delayed recognition of these conditions (in order of months to years). In addition, association with neoplastic disease for some of the patients complicates the work up and final diagnosis. Since discovery of VGKC antibodies, some conditions, previously considered only for empirical treatment, received reasonable understanding of pathogenesis based on interaction of the autoantibody with VGKC receptor on the cell membrane in central and peripheral nervous system. Considering autoimmune component as the primary cause of LE, NMT and MVS, different immunotherapies have been used including steroids, cyclosporine, azathioprine, mycophenolate mofetil, IVIG, and TPE in addition to symptomatic treatment (e.g., antiseizure medication).

Rationale for therapeutic apheresis

There is a clear rationale for the use of TPE in the autoimmune condition. The multiple case reports showed that VGKC antibodies decrease with TPE, and this is associated with clinical improvement. Wong et al. reported in the open label prospective study immunotherapy protocol consisting of IV methylprednisolone (1 g/day for 3 days), TPE (50 mL/kg; 5 treatments over 7–10 days typically after completion of IV methylprednisolone but occasionally used concurrenty), followed by IVIG (2 g/kg over 5 days) and maintenance therapy with oral prednisolone (1 mg/kg). Using this regimen on 9 patients (first three patients also received MMF at 2 g/day) they reported improvement in all treated patients with clinical remission ranging from 4 to 40 months and remission of changes on MRI. The clinical improvement was accompanied by significantly decreased VGKC levels. Vincent et al. reported on two center retrospective analysis of 10 patients with LE. TPE was administered in 7 patients in conjunction with steroids and IVIG. The overall response rate for the patients who received TPE was 86% with 57% reporting definitive and 29% reporting slight improvement. It was noted that early steroid administration was associated with faster decrease in antibody titers. Jaben et al. reported on retrospectively identified five patients with neurological symptoms and VGKC antibodies treated with TPE. There was a durable clinical response in 60% of these patients. These data suggest that there is beneficial and, possibly, synergistic effect of TPE in the setting of these neurological conditions.

Technical notes

Some investigators (see above) suggest using 50 mL/kg plasma exchange, however, there are no strong data to support this volume. The patients who present with seizures should be adequately protected against self-injury if seizure activity occurs during performance of apheresis procedure. Some of the patients, due to their memory loss and other neuropsychiatric symptoms, might not be good historians and involvement of family members in evaluation of the response to treatment in addition to formal evaluation can be helpful. These patients may also exhibit emotional and physical outburst, hence additional precautions might be necessary for the staff until patient reaction to the environment and treatment is established.

Volume treated: 1–1.5 TPV	**Frequency:** Every other day
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

Five to seven TPE procedures over 7–14 days are recommended. The assessment of VGKC antibody levels is suggested after the series of treatments to evaluate the response. It has been shown that the level of the antibody correlates with severity of the symptoms. The response to the treatment might be delayed, so additional treatments beyond seven are not generally recommended.

References [1507–1536]

*As of January 10, 2013 using PubMed and the MeSH search terms voltage gated potassium channel antibodies, limbic encephalitis, acquired neuromyotonia, Morvan's syndrome, plasmapheresis, plasma exchange, or apheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

WILSON DISEASE

Incidence: 3/100,000	**Condition** Fulminant	**Procedure** TPE	**Recommendation** Grade 1C	**Category** I
# of reported patients*: <100				
RCT	**CT**	**CS**	**CR**	
0	0	0	17 (18)	

Description of the disease

Autosomal recessive genetic disorder of the *ATP7B* gene, a copper transporting p-type ATPase protein mainly expressed in hepatocytes. ATP7B protein deficiency impairs biliary copper excretion, resulting in copper accumulation in the liver, brain, cornea and kidney. The incorporation of copper into ceruloplasmin is also impaired. Patients with Wilson's disease may present with hepatic, neurologic, and/or hematological manifestations due to copper released into the circulation from dying hepatocytes. The diseases most commonly presents between ages 5–35 years. Presentation is variable depending on age. In infants and children it is most commonly silent deposit of copper in the liver, teenagers present more with liver disease while adults present with neurological symptoms. The spectrum of liver disease includes asymptomatic liver function tests abnormalities, hepatitis, cirrhosis and acute liver failure. Neurological symptoms include Parkinsonism in most cases, dystonia, cerebellar and pyramidal symptoms. A history of behavioral disturbances is present in half of patients with neurological disease. The appearance of Kayser-Fleischer ring (copper deposits in the outer rim of the cornea) and direct antiglobulin test (DAT) negative hemolytic anemia are relatively common. The hemolysis appears to be primarily due to copper-induced oxidant stress to red cell enzyme pathways and damage to their membrane. Mortality rates are high when fulminant hepatic failure is accompanied by hemolytic crisis. No laboratory test is diagnostic but suggestive results include low serum ceruloplasmin, increase 24-h urinary copper excretion, elevated serum copper. The "gold standard" for diagnosis remains liver biopsy with elevated hepatic parenchymal copper content. Most recently, a molecular genetic testing became available.

Current management/treatment

Earlier detection led to treatment initiation to prevent disease progression and reverse pathologic findings if present as well as screening in first degree relatives. Low-copper diets are recommended. Zinc acetate stimulates metallothioneine. This protein in intestinal mucosal cells reduces absorption of both dietary copper as well as copper in the enterohepatic circulation. Zinc has proven efficacy for this disease and is essentially nontoxic. For patients with hepatitis or cirrhosis, but without evidence of hepatic decompensation or neurologic/psychiatric symptoms, it is the therapy of choice. Zinc is also first choice for maintenance therapy and in presymptomatic, pediatric and pregnant patients. All asymptomatic patients should be treated prophylactically, since the disease is close to 100% penetrant. Urinary excretion can be increased by chelation therapy with penicillamine or with trientine. Penicillamine used to be the primary copper chelator agent; however, its full effects may take months, and it currently plays a minor role because of its toxicity. If penicillamine is given, it should always be accompanied by 25 mg/d of pyridoxine. Trientine is a less toxic chelator and can replace penicillamine when a chelator is indicated. Those chelators can be used as temporizing agents to treat enormous release of copper into the blood stream in fulminant hepatic failure with renal failure; however substantial removal is not achieved for at least 1–3 months. Other methods have been used to reduce copper load in an attempt to stabilize patients. Those methods have included hemofiltration, albumin dialysis and the Molecular Adsorbents Recirculating System (MARS).

Liver transplantation is potentially curative and is the main stay of therapy for patients with fulminant hepatic failure. The severity is estimated using prognostic score which is based on combination of laboratory values, most commonly serum bilirubin, serum aspartate transferase (AST) and coagulation status (INR/PT). Liver transplantation reveres most of the clinical and biochemical pathological manifestations of the disease within a few months. For initial neurologic therapy, tetrathiomolybdate is emerging as the drug of choice because of its rapid action, preservation of neurologic function, and low toxicity. Penicillamine and trientine should be avoided since they often worsen neurologic disease if used as initial therapy. Anticopper therapy must be lifelong. Future directions might include gene therapy and hepatocyte cell transplantation which has only been tested in animals models to date.

Rationale for therapeutic apheresis

Fulminant hepatic failure due to Wilson disease is characteristically accompanied by a severe DAT- negative hemolytic anemia and multiorgan failure with rapid clinical deterioration (Wilson's crisis), and is nearly always fatal without liver transplantation. However, donor organs for liver transplantation are not always available and temporizing treatments must be aimed at treating the release of the massive amounts of copper into the circulation. In this scenario, TPE can be beneficial as it can rapidly remove significant amount of copper. Decreased serum copper would decrease hemolysis, prevent progression of renal failure and provide clinical stabilization. An average of 20 mg of copper can be removed from the circulation by a TPE treatment. Thus, in most reported cases, TPE was used as a bridge to liver transplantation. Interestingly, in a recent case report, successful use of TPE led to elimination of the need for urgent transplantation. In addition, the widespread availability of TPE over MARS or equivalent technology makes it a more reasonable choice of therapy.

Technical notes

Replacement of the patient's plasma with fresh frozen plasma provides additional coagulation factors and rapidly corrects coagulopathy. A combination of plasma and albumin is also possible. Use of Albumin alone will worsen coagulopathy.

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

Duration and discontinuation/number of procedures

The reduction in serum copper in most case reports had been achieved rapidly and maintained after the first two treatments. However, daily TPE can be beneficial if the patient has acute hepatic failure with coagulopathy until liver transplantation is performed. The specific laboratory tests for the disease e.g., serum copper, 24-h urinary copper excretion are not routine testing thus are not helpful to guide effectiveness and the frequency of the treatment. In most cases judgment might be based on clinical parameters and routine testing, that is, improved encephalopathy, controlled hemolysis, decrease in liver function tests abnormalities, etc.

References: [1537–1543]

*As of April 22, 2012 using PubMed and the MeSH search terms Wilson's disease and TPE, plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

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