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

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The American Society for Apheresis (ASFA) Journal of Clinical Apheresis (JCA) Special Issue Writing Committee is charged with reviewing, updating, and categorizing indications for the evidence-based use of therapeutic apheresis in human disease. Since the 2007 JCA Special Issue (Fourth Edition), the Committee has incorporated systematic review and evidence-based approaches in the grading and categorization of apheresis indications. This Seventh Edition of the JCA Special Issue continues to maintain this methodology and rigor to make recommendations on the use of apheresis in a wide variety of diseases/conditions. The JCA Seventh Edition, like its predecessor, has consistently applied the category and grading system definitions in the fact sheets. The general layout and concept of a fact sheet that was used since the fourth edition has largely been maintained in this edition. Each fact sheet succinctly summarizes the evidence for the use of therapeutic apheresis in a specific disease entity. The Seventh Edition discusses 87 fact sheets (14 new fact sheets since the Sixth Edition) for therapeutic apheresis diseases and medical conditions, with 179 indications, which are separately graded and categorized within the listed fact sheets. Several diseases that are Category IV which have been described in detail in previous editions and do not have significant new evidence since the last publication are summarized in a separate table. The Seventh Edition of the JCA Special Issue serves as a key resource that

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INTRODUCTION

It is with great pleasure that we present to you the Journal of Clinical Apheresis (JCA) Special Issue 2016 (also known as the Seventh Edition of the JCA Special Issue). After >2 years of engaging work and the rigorous critical review of fact sheets contained herein, we believe that this document will appeal to both practitioners with a focus in the area of apheresis medicine and other physicians who may need to use therapeutic apheresis occasionally for the care of their patients. This fourth iteration of evidence-based ASFA categories is based on a stringent review of up-to-date literature, analysis of the quality of evidence, and the strength of recommendation derived from this evidence.

To clarify terminology used throughout this document, "Disease" refers to a specific disease or medical condition (e.g., myasthenia gravis [disease]; liver transplantation [medical condition]) and is the pathology discussed in the fact sheet. "Indication" refers to the use of apheresis in specific situations encountered in the disease (e.g., antibody-mediated rejection [indication] in the setting of cardiac transplantation [disease]).

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 [strong (1) vs. weak (2)]; and finally, it provides comprehensive, yet succinct information easily shared with healthcare providers requesting information on the potential utility of apheresis in a given clinical setting. This Special Issue is a compilation of fact sheets for diseases which are assigned ASFA categories I through IV. Given the utility of the table format used in prior editions to summarize disease name, special condition(s) (indications), 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 adsorptive cytapheresis, therapeutic plasma exchange (TPE), erythrocytapheresis, red blood cell (RBC) exchange, thrombocytapheresis, leukocytapheresis, filtration-based selective apheresis, extracorporeal photopheresis (ECP), immunoadsorption (IA), LDL apheresis, adsorptive cytapheresis, B_2 microglobulin column, high-volume plasma exchange (HVP), and rheopheresis.

The 2016 JCA Special Issue Writing Committee consisted of 10 ASFA members from diverse fields including Transfusion Medicine/Apheresis, Hematology/Oncology, Pediatrics, Nephrology, and Critical Care and from diverse geographies throughout the United States and Europe. Indications 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 disease incidence, description, management, rationale for the use of apheresis, technical notes such as volumes treated, replacement fluids used, treatment frequency, optimal duration of therapeutic apheresis, and references. Additional diseases included in the Seventh Edition were based on input from comments received from the membership of ASFA. The first draft of fact sheets was reviewed by two other Committee members, followed by an external expert 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 and Sixth Editions, with consistent application of evaluation criteria [1,2].

Fourteen New Diseases are Included in the JCA Special issue 2016. The new diseases included are presented in Table I. Some previously published fact sheets were renamed, in keeping with new understanding of the pathogenesis of the diseases categorized. For example, aHUS and HUS were renamed thrombotic microangiopathy (TMA), complement mediated, and TMA, Shiga toxin mediated, respectively. Similar to the Sixth Edition, if apheresis was used in more than one clinical setting within the same disease, each condition in which it was used was treated as a separate indication and assigned a separate recommendation grade and category. Several fact sheets such as those on lung and liver

TABLE I. New Diseases Included in the JCA Special issue 2016

1. Atopic (neuro-) dermatitis (atopic eczema), recalcitrant
2. Cardiac neonatal lupus
3. Complex regional pain syndrome
4. Erythropoietic porphyria, liver disease
5. Hashimoto's encephalopathy: Steroid-responsive encephalopathy associated with autoimmune thyroiditis
6. HELLP syndrome
7. Hematopoietic stem cell transplantation, HLA desensitization
8. Hemophagocytic lymphohistiocytosis; Hemophagocytic syndrome; Macrophage activating syndrome
9. N-methyl D-aspartate receptor antibody encephalitis
10. Prevention of RhD allloimmunization after RBC exposure
11. Progressive multifocal leukoencephalopathy associated with nataluziamab
12. Pruritus due to hepatobiliary diseases
13. Thrombotic microangiopathy, coagulation mediated
14. Vasculitis

TABLE II. Category Definitions for Therapeutic Apheresis

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.
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
III	Optimum role of apheresis therapy is not established. Decision making should be individualized.
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.

transplantation saw an expansion of such indications. The total number of diseases and indications addressed in the Seventh Edition are 87 and 179, respectively.

METHODOLOGY

Evidence-Based Approach

The JCA Special Issue 2007 (Fourth Edition) incorporated evidence-based medicine into well-defined and widely accepted ASFA Categories and quality of the evidence [3]. In the JCA 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 JCA Special Issue 2013 (Sixth Edition), this was further refined to provide information on categorization, and strength of recommendation based on the GRADE system, which takes methodological quality of supporting evidence into

account, whereas eliminating the need for "Level of Evidence" information used in previous edition. The current edition follows the format used in the Sixth Edition and provides information on ASFA category (Table II) and quality of supporting evidence that forms the basis of the recommendation (Table III).

ASFA Categories

The definition of the four ASFA categories in the Seventh Edition remains unchanged from the definition used in the Sixth Edition (Table II). 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 Writing Committee recognizes the challenges in assessing study quality and translating recommendations into clinical practice. A commonly used system to assess the quality of published evidence, The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, for grading evidence is generally user friendly as evidenced in multiple publications [4–9]. In the Fifth and Sixth Editions, 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 Seventh Edition. Table III contains abbreviated principles of grading recommendations derived from Guyatt et al. [4,9]. It is

TABLE III. Grading Recommendations Adopted from Guyatt et al. [4,9]

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

Fig. 1.   Explanation of the fact sheet used in the ASFA Special Issue, Seventh Edition (2016).

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 United States and other selected geographic regions, when appropriate. In some instances, when the incidence varies between genders, ethnicity, or race, this information is 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 indication section refers to the use of apheresis in specific situations encountered in the disease (e.g., antibody-mediated rejection [indication] in the setting of cardiac transplantation [disease]).

D   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 transplantation), more than one type of therapeutic apheresis modality is listed.

E   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 the level of clinical recommendation.

F   The ASFA category is listed for each therapeutic apheresis modality discussed.

G   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 therapeutic apheresis. However, the number of patients treated is often less important than the quality of the scientific reports.

H   This section is used when there are several different therapeutic apheresis procedures used, and it was necessary to subdivide available scientific reports, as well as in the situation when different subsets of patients are being analyzed. Not all entries will have this section.

Fig 1.   *(Continued)*

I   Randomized controlled trials (RCT): The number of RCTs and the total number of patients studied. For example, 4 (250) indicates that there were four RCTs with 250 enrolled patients. The patient count includes all patients irrespective of randomization to either treatment group (with therapeutic apheresis) or the control arm. 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 of two arms and one randomized study with 75 patients in each of two arms is denoted as 3 (350).

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

K   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 56 reported patients.

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

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

N   This section provides a brief description of therapeutic modalities available to treat the disease. The committee attempted to cover all reasonable modalities (e.g., medications and surgical procedures); however, this section is not intended to provide extensive discussion of any specific 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.

O   This section discusses a rationale for therapeutic apheresis use in the disease and summarizes the evidence in this area.

P   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 may have specific technical notes.

Q   This section specifies commonly used volumes of plasma or blood treated.

R   The proposed frequency of treatment is listed here. The frequency reported was typically based on the data from published reports. However, in some settings, because of significant variability in treatment schedules reported by different groups, 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 discretion to the treating physician.

S   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 vs. solvent detergent plasma vs. cryoprecipitate-poor 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).

T   This section provides basic criteria for discontinuation of apheresis procedures (i.e., end points/outcomes, both clinical and laboratory). In some instances, the number of procedures/series which may be reasonably used in the particular clinical situation is suggested based on currently available data. The committee believes that a thoughtful approach to patient management is required to establish reasonable and scientifically sound criteria for discontinuation of treatment.

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

important to note that the grade can be used in support or against the use of the therapeutic intervention. In addition, previously designated weak recommendations for diseases/conditions, such as Grade 2C, are more likely to be affected by additional evidence of higher quality than diseases that already have strong recommendations (e.g., Grade 1A). The quality of published evidence can be affected by a number of factors [9]. As an example, the quality of evidence based on a randomized controlled trial (RCT) can be significantly diminished by poor quality of planning and implementation of RCTs suggesting a high likelihood of bias, inconsistency of results, indirectness of evidence, and/or sparse outcome data. The members of the Committee carefully took these variables into consideration while grading and categorizing disease indications.

Design of the Fact Sheet

The 2016 JCA Special Issue Writing Committee made no changes in the design of the fact sheet from the Sixth Edition based on positive feedback regarding the fact sheet format. 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 references provided are not meant to be exhaustive but rather serve as a starting point in a search for more information. Authors of fact sheets were asked to try to limit the number of key references to 20, unless it was critically important to provide additional references to substantiate recommendations made in the fact sheet.

ASFA Category Assignments for 2016

The process for ASFA category assignment developed for previous editions has been maintained and enhanced by stringent application of evidence-based criteria to ensure consistency within and across fact sheets. The JCA Special Issue Writing Committee strived to be comprehensive and systematic in assembling objective evidence for disease indications, with strength of recommendation based on the quality of the
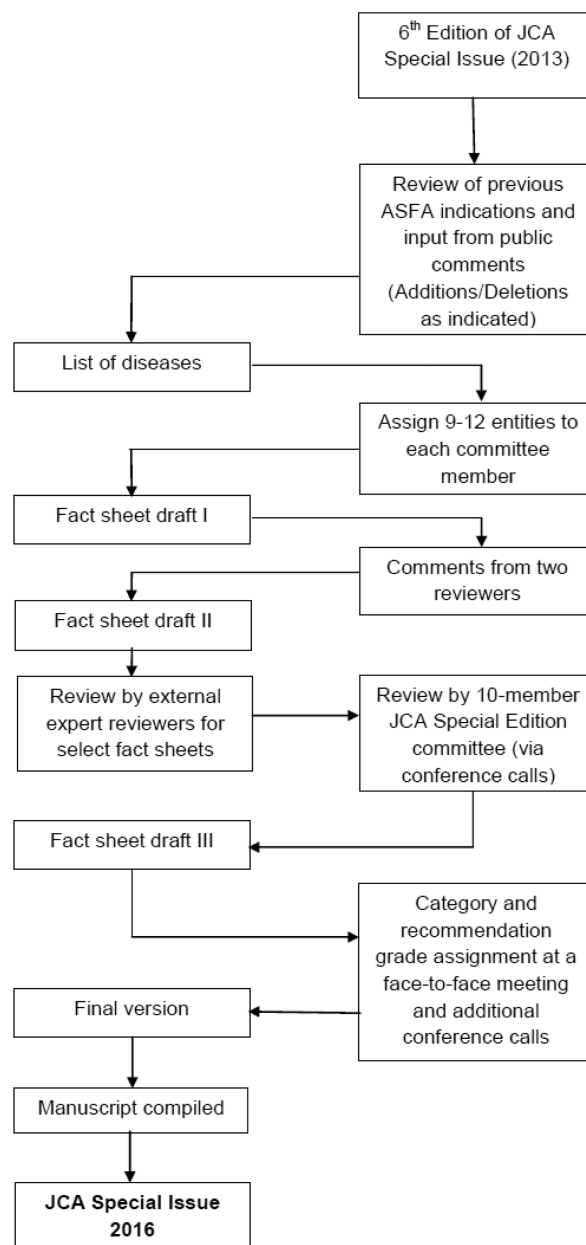
Fig. 2. Systematic approach to ASFA category and recommendation grade assignment, fact sheet generation, and revision in the JCA Special Issue 2016.

evidence [1–3]. The 2016 JCA Special Issue Writing Committee consisting of 10 ASFA members was established in 2014, and this group was asked to review, revise, and amend indications for the use of therapeutic apheresis in a very wide range of diseases. The membership of ASFA was also queried for new indications that had published experience with apheresis therapy but had previously not been categorized by the JCA Special Issue Writing Committee.

The process of developing new and amending old fact sheets 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 9 to 12 diseases each to review.

At a minimum, the review consisted of identifying all articles published in the English language, which described the use of therapeutic apheresis in the disease state. For suggested new diseases, one or more Committee members evaluated the available literature for evidence for the use of therapeutic apheresis in the disease entity. The following conditions were deemed to have inadequate information to assign fact sheets: Platelet transfusion allorefractoriness, mechanical red cell hemolysis, methemoglobulinemia, autoimmune myofasciitis, recurrent pregnancy loss, antisynthetase syndrome, pancreatic transplantation, and composite tissue transplantation. New diseases identified for inclusion in the Seventh Edition are

TABLE IV. Category and Grade Recommendations for Therapeutic Apheresis

Disease name	TA Modality	Indication	Category	Grade	Page
Acute disseminated encephalomyelitis	TPE	Steroid Refractory	II	2C	163
Acute inflammatory demyelinating polyradiculoneuropathy/ Guillain-Barre syndrome	TPE TPE	Primary Treatment After IVIG	I III	1A 2C	165
Acute liver failure	TPE TPE-HV		III I	2B 1A	167
Age related macular degeneration, dry	Rheopheresis		I	1B	169
Amyloidosis, systemic	β_2 microglobulin column TPE		II IV	2B 2C	171
ANCA-associated rapidly progressive glomerulonephritis (Granulomatosis with polyangiitis; and Microscopic Polyangiitis)	TPE TPE TPE	Dialysis dependence DAH Dialysis independence	I I III	1A 1C 2C	173
Anti-glomerular basement membrane disease (Goodpasture's syndrome)	TPE TPE TPE	Dialysis dependence, no DAH DAH Dialysis independence	III I I	2B 1C 1B	175
Aplastic anemia, pure red cell aplasia	TPE TPE	Aplastic anemia Pure red cell aplasia	III III	2C 2C	177
Atopic (neuro-) dermatitis (atopic eczema), recalcitrant	ECP IA TPE		III III III	2C 2C 2C	179
Autoimmune hemolytic anemia; WAIHA; cold agglutinin disease	TPE TPE	Severe WAIHA Severe cold agglutinin disease	III II	2C 2C	181
Babesiosis	RBC exchange	Severe	II	2C	183
Burn shock resuscitation	TPE		III	2B	185
Cardiac neonatal lupus	TPE		III	2C	187
Cardiac transplantation	ECP ECP TPE TPE	Cellular/recurrent rejection Rejection prophylaxis Desensitization Antibody mediated rejection	II II II III	1B 2A 1C 2C	189
Catastrophic antiphospholipid syndrome	TPE		II	2C	191
Chronic focal encephalitis (Rasmussen Encephalitis)	TPE		III	2C	193
Chronic inflammatory demyelinating polyradiculoneuropathy	TPE		I	1B	195
Coagulation factor inhibitors	TPE TPE IA IA	Alloantibody Autoantibody Alloantibody Autoantibody	IV III III III	2C 2C 2B 1C	197
Complex regional pain syndrome	TPE	Chronic	III	2C	199
Cryoglobulinemia	TPE IA	Symptomatic/severe Symptomatic/severe	II II	2A 2B	201
Cutaneous T-cell lymphoma; mycosis fungoides; Sezary syndrome	ECP ECP	Erythrodermic Non-erythrodermic	I III	1B 2C	203
Dermatomyositis/polymyositis	TPE ECP		IV IV	2B 2C	205
Dilated cardiomyopathy, idiopathic	IA TPE	NYHA II-IV NYHA II-IV	II III	1B 2C	207
Erythropoietic porphyria, liver disease	TPE RBC Exchange		III III	2C 2C	209

TABLE IV. *Continued*

Disease name	TA Modality	Indication	Category	Grade	Page
Familial hypercholesterolemia	LDL apheresis	Homozygotes	I	1A	211
	LDL apheresis	Heterozygotes	II	1A	
	TPE	Homozygotes with small blood volume	II	1C	
Focal segmental glomerulosclerosis	TPE	Recurrent in transplanted kidney	I	1B	213
	LDL apheresis	Steroid resistant in native kidney	III	2C	
Graft-versus-host disease	ECP	Skin (chronic)	II	IB	216
	ECP	Non-skin (chronic)	II	IB	
	ECP	Skin (acute)	II	1C	
	ECP	Non-skin(acute)	II	1C	
Hashimoto's encephalopathy: Steroid-responsive encephalopathy associated with autoimmune thyroiditis	TPE		II	2C	219
HELLP syndrome	TPE	Postpartum	III	2C	221
	TPE	Antepartum	IV	2C	
Hematopoietic stem cell transplantation, ABO Incompatible	TPE	Major HPC, Marrow	II	1B	223
	TPE	Major HPC, Apheresis	II	2B	
	RBC exchange	Minor HPC, Apheresis	III	2C	
Hematopoietic stem cell transplantation, HLA desensitization	TPE		III	2C	225
Hemophagocytic lymphohistiocytosis; Hemophagocytic syndrome; Macrophage activating syndrome	TPE		III	2C	227
Henoch-Schönlein purpura	TPE	Crescentic	III	2C	229
	TPE	Severe extrarenal disease	III	2C	
Heparin induced thrombocytopenia & thrombosis	TPE	Pre-cardiopulmonary bypass	III	2C	231
	TPE	Thrombosis	III	2C	
Hereditary hemachromatosis	Erythrocytapheresis		I	IB	233
Hyperleukocytosis	Leukocytapheresis	Symptomatic	II	1B	235
	Leukocytapheresis	Prophylactic or secondary	III	2C	
Hypertriglyceridemic pancreatitis	TPE		III	2C	237
Hyperviscosity in monoclonal gammopathies	TPE	Symptomatic	I	1B	239
	TPE	Prophylaxis for rituximab	I	1C	
Immune thrombocytopenia	TPE	Refractory	III	2C	241
	IA	Refractory	III	2C	
Immunoglobulin A nephropathy	TPE	Crescentic	III	2B	243
	TPE	Chronic progressive	III	2C	
Inflammatory bowel disease	Adsorptive cytapheresis	Ulcerative colitis	III/II	1B/2B	245
	Adsorptive cytapheresis	Crohn's Disease	III	1B	
	ECP	Crohn's Disease	III	2C	
Lambert-Eaton myasthenic syndrome	TPE		II	2C	247
Lipoprotein (a) hyperlipoproteinemia	LDL apheresis		II	1B	249
Liver transplantation	TPE	Desensitization, ABOi LD	I	1C	251
	TPE	Desensitization, ABOi DD	III	2C	
	TPE	Antibody mediated rejection (ABOi & HLA)	III	2C	
Lung transplantation	ECP	Bronchiolitis obliterans syndrome	II	1C	253
	TPE	Antibody mediated rejection	III	2C	
	TPE	Desensitization	III	2C	
Malaria	RBC exchange	Severe	III	2B	255
Multiple sclerosis	TPE	Acute CNS inflammatory demyelinating	II	1B	257
	IA	Acute CNS inflammatory demyelinating	III	2C	
	TPE	Chronic progressive	III	2B	

TABLE IV. *Continued*

Disease name	TA Modality	Indication	Category	Grade	Page
Myasthenia gravis	TPE	Moderate-severe	I	1B	259
	TPE	Pre-thymectomy	I	1C	
Myeloma cast nephropathy	TPE		II	2B	261
Nephrogenic systemic fibrosis	ECP		III	2C	263
	TPE		III	2C	
Neuromyelitis optica spectrum disorders	TPE	Acute	II	1B	265
	TPE	Maintenance	III	2C	
N-methyl D-aspartate receptor antibody encephalitis	TPE		I	1C	267
Overdose, envenomation and poisoning	TPE	Mushroom poisoning	II	2C	269
	TPE	Envenomation	III	2C	
	TPE	Drug overdose/poisoning	III	2C	
Paraneoplastic neurological syndromes	TPE		III	2C	271
	IA		III	2C	
Paraproteinemic demyelinating neuropathies/chronic acquired demyelinating polyneuropathies	TPE	Anti-MAG neuropathy	III	1C	273
	TPE	Multifocal Motor Neuropathy	IV	1C	
	TPE	IgG/IgA	I	1B	
	TPE	IgM	I	1C	
	TPE	Multiple myeloma	III	2C	
	IA	IgG/IgA/IgM	III	2C	
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; Sydenham's chorea	TPE	PANDAS exacerbation	II	1B	275
	TPE	Sydenham's chorea, severe	III	2B	
Pemphigus vulgaris	TPE	Severe	III	2B	277
	ECP	Severe	III	2C	
	IA	Severe	III	2C	
Peripheral vascular diseases	LDL apheresis		II	1B	279
Phytanic acid storage disease (Refsum's disease)	TPE		II	2C	281
	LDL apheresis		II	2C	
Polycythemia vera; erythrocytosis	Erythrocytapheresis	Polycythemia vera	I	1B	283
	Erythrocytapheresis	Secondary erythrocytosis	III	1C	
Post transfusion purpura	TPE		III	2C	285
Prevention of RhD alloimmunization after RBC exposure	RBC exchange	Exposure to RhD(+) RBCs	III	2C	287
Progressive multifocal leukoenchephalopathy associated with natalizumab	TPE		I	1C	289
Pruritus due to hepatobiliary diseases	TPE	Treatment resistant	III	1C	291
Psoriasis	ECP		III	2B	293
	Adsorptive cytapheresis	Disseminated pustular	III	2C	
	Lymphocytapheresis		III	2C	
	TPE		IV	2C	
Red cell alloimmunization in pregnancy	TPE	Prior to IUT availability	III	2C	295
Renal transplantation, ABO compatible	TPE/IA	Antibody mediated rejection	I	1B	297
	TPE/IA	Desensitization, LD	I	1B	
	TPE/IA	Desensitization, DD	III	2C	
Renal transplantation, ABO incompatible	TPE/IA	Desensitization, LD	I	1B	299
	TPE/IA	Antibody medicated rejection	II	1B	
	TPE/IA	A_2/A_2B into B, DD	IV	1B	
Scleroderma (systemic sclerosis)	TPE		III	2C	301
	ECP		III	2A	
Sepsis with multi-organ failure	TPE		III	2B	303

TABLE IV. *Continued*

Disease name	TA Modality	Indication	Category	Grade	Page
Sickle cell disease, acute	RBC Exchange	Acute stroke	I	1C	305
	RBC Exchange	Acute chest syndrome, severe	II	1C	
	RBC Exchange	Priapism	III	2C	
	RBC Exchange	Multiorgan failure	III	2C	
	RBC Exchange	Splenic/ hepatic sequestration; intrahepatic cholestasis	III	2C	
Sickle cell disease, non-acute	RBC exchange	Stroke prophylaxis/iron overload prevention	I	1A	307
	RBC exchange	Recurrent vaso-occlusive pain crisis	III	2C	
	RBC exchange	Pre- operative management	III	2A	
	RBC exchange	Pregnancy	III	2C	
Stiff-person syndrome	TPE		III	2C	309
Sudden sensorineural hearing loss	LDL apheresis		III	2A	311
	Rheopheresis		III	2A	
	TPE		III	2C	
Systemic lupus erythematosus	TPE	Severe	II	2C	313
	TPE	Nephritis	IV	1B	
Thrombocytosis	Thrombocytapheresis	Symptomatic	II	2C	315
	Thrombocytapheresis	Prophylactic or secondary	III	2C	
Thrombotic microangiopathy, coagulation mediated	TPE	*THBD* mutation	III	2C	317
Thrombotic microangiopathy, complement mediated	TPE	Complement factor gene mutations	III	2C	319
	TPE	Factor H autoantibodies	I	2C	
	TPE	MCP mutations	III	1C	
Thrombotic microangiopathy, drug associated	TPE	Ticlopidine	I	2B	321
	TPE	Clopidogrel	III	2B	
	TPE	Calcineurin inhibitors	III	2C	
	TPE	Gemcitabine	IV	2C	
	TPE	Quinine	IV	2C	
Thrombotic microangiopathy, hematopoietic stem cell transplantation associated	TPE		III	2C	323
Thrombotic microangiopathy, Shiga toxin mediated	TPE/IA	Severe neurological symptoms	III	2C	325
	TPE	Streptococcus pneumoniae	III	2C	
	TPE	Absence of severe neurological symptoms	IV	1C	
Thrombotic thrombocytopenic purpura	TPE		I	1A	327
Thyroid storm	TPE		III	2C	329
Toxic epidermal necrolysis	TPE	Refractory	III	2B	331
Vasculitis	TPE	HBV-PAN	II	2C	333
	TPE	Idiopathic PAN	IV	1B	
	TPE	EGPA	III	1B	
	Adsorption granulocytapheresis	Behcet's disease	II	1C	
	TPE	Behcet's disease	III	2C	
Voltage-gated potassium channel antibodies	TPE		II	2C	335
Wilson's disease, fulminant	TPE	Fulminant	I	1C	337

DAH = diffuse alveolar hemorrhage; DD = deceased donor; EGPA = eosinophilic granulomatosis with polyangiitis; LD = living donor; PAN = polyarteritis nodasa; WAIHA = warm autoimmune hemolytic anemia.

presented in Table I. Step III consisted of circulating the first draft (Draft I) of the factsheet to two other members of the Committee for critique and comment. In some cases, Draft I was also sent to external subject matter experts for comments (see Acknowledgments section below). On the basis of these comments, the author created Draft II. In Step IV, all fact sheets were discussed and then finalized. Each disease was assigned an ASFA
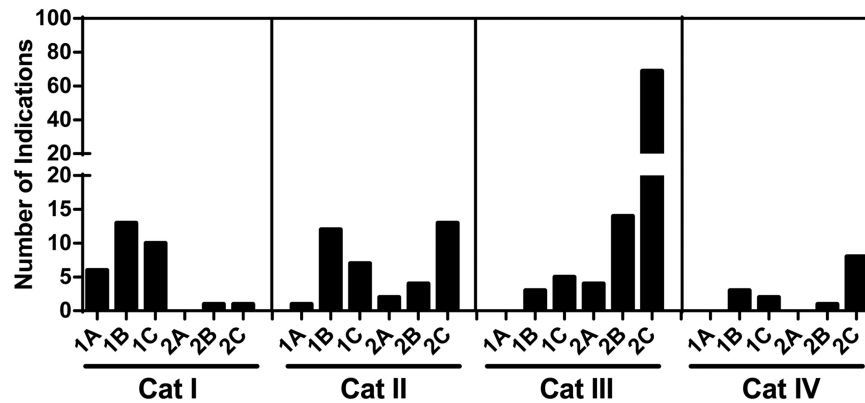
Fig. 3.   The ASFA category indications and the recommendation grade in the JCA Special Issue 2016.

TABLE V.   Category IV Recommendations for Therapeutic Apheresis[a]

Disease	Procedure	Full Factsheet
Amyotrophic lateral sclerosis	TPE	JCA Sp Ed (2013) [2]
Inclusion body myositis	TPE, LCP	JCA Sp Ed (2013) [2]
POEMS syndrome	TPE	JCA Sp Ed (2013) [2]
Rheumatoid arthritis	TPE	JCA Sp Ed (2010) [1]
Schizophrenia	TPE	JCA Sp Ed (2013) [2]

[a]This table summarizes diseases where published evidence demonstrates or suggests apheresis to be ineffective or harmful (i.e., Category IV). This table excludes diseases in which apheresis may be ineffective in some settings, but may potentially be used in other settings in the same disease (e.g., TMA, Shiga toxin mediated), or where one type of apheresis may be ineffective, whereas a different apheresis modality may potentially be useful in the same disease. In addition, Category IV fact sheets that have significant new information available that add to the body of evidence to make categorization recommendations have also been excluded from this table. Such diseases continue to be described in a full fact sheet format in the current JCA Special Edition (Table IV).

category and grade of recommendation at a face-to-face meeting and several conference calls of the Committee in 2015–2016. The category assignment and recommendation grade were based on literature review and determined by consensus by the Writing Committee. Members of the Committee were encouraged to use "McLeod's Criteria" [10] to assess the indication for which apheresis treatment was being evaluated for efficacy. We encourage practitioners of apheresis medicine to carefully use these criteria when considering the use of therapeutic apheresis in rare medical conditions which may yet to be categorized by JCA Special Issue Writing Committee.

ASFA category and grade of recommendation for 87 diseases are summarized in Table IV. As in previous edition fact sheets, if more than one type of apheresis modality was used or if apheresis was used in more than one clinical setting in the same disease state, each was treated as a separate indication and each indication was assigned a recommendation grade and category. As an example, the lung transplantation fact sheet now

TABLE VI.   General Issues to Consider When Evaluating a New Patient for Therapeutic Apheresis

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 a 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, and routine). The location where the therapeutic apheresis will take place should also be addressed (e.g., intensive care unit, medical word, operating room, and 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]Fact Sheet for each disease could be helpful in addressing these issues.

TABLE VII.   Apheresis Procedure Definitions

Procedure/term	Definition
Adsorptive cytapheresis	A therapeutic procedure in which blood of the patient is passed through a medical device, which contains a column or a 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 one or more components of blood and returns the remainder with or without extracorporeal treatment or replacement of the separated component.
B_2 microglobulin column	The B_2 microglobulin apheresis column contains porous cellulose beads specifically designed to bind to B_2 microglobulin as the patient's blood passes over the beads.
High-volume plasma exchange (HVP)	HVP is defined as an exchange of 15% of ideal body weight (representing 8–12 L); patient plasma was removed at a rate of 1–2 L per hour with replacement with plasma in equivalent volume.
Extracorporeal photopheresis (ECP)	A therapeutic procedure in which the buffy coat is separated from the patient's blood, treated extracorporeally with a photoactive compound (e.g., psoralens) and exposed to ultraviolet A light then 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 red blood cells from other components of blood. The red blood cells 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 on size. Depending on 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 on 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 white blood cells (e.g., leukemic blasts or granulocytes), collects the selected cells, and returns the remainder of the patient's or the donor's blood with or without the addition of replacement fluid such as colloid and/or crystalloid solution. This procedure can be used therapeutically or in the 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 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 a 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 plasma from other components of blood and the plasma is removed (i.e., less than 15% of total plasma volume) without the use of colloid replacement solution. This procedure is used to collect plasma for blood components or plasma derivatives.
Plateletapheresis	A procedure in which blood of the donor is passed through a medical device which separates platelets, collects the platelets, and returns the remainder of the donor's blood. This procedure is used in the 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 red blood cells from other components of blood. The patient's red blood cells are removed and replaced with donor red blood cells and colloid solution.
Rheopheresis	A therapeutic procedure in which blood of the patient is passed through a medical device which separates high-molecular-weight plasma components such as fibrinogen, $\alpha2$-macroglobulin, low-density lipoprotein cholesterol, and IgM 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 using 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 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 platelets, removes the platelets, and returns the remainder of the patient's blood with or without the addition of replacement fluid such as colloid and/or crystalloid solution.

includes three different conditions: desensitization, antibody-mediated rejection, and bronchiolitis obliterans syndrome. Providing this level of detail in the fact sheet is expected to provide adequate clinical practice information to assist in appropriate management of patients with these complex disease states.

The relationship between ASFA categories and recommendation grades is illustrated in Figure 3. There is a

significant expansion in the number of indications (relative to the number of diseases categorized) and is accounted for by some diseases having several categories and recommendation grades due to multiple indications within the same disease or multiple apheresis modalities used to treat the same disease. In a minority of diseases, there was only a single indication, for example, TPE in Lambert-Eaton myasthenic syndrome. Thus, a total of 87 diseases and 179 indications are categorized (Fig. 3). The number of Category I, II, III, and IV indications are 31, 39, 96, and 13, respectively (Table IV and Fig. 3). The majority of Category I indications have recommendation Grades of 1A–C (29/31). Category II indications are spread through the entire spectrum of recommendation grades with roughly half (20) with recommendation Grade 1A–C, and the remainder (19) with recommendation Grade 2A–C. As in prior editions, the vast majority (70/96) of Category III indications have recommendation Grade 2C (weak recommendation with low/very low-quality evidence). The Category IV indications include 13 listed in full factsheets in this edition, and several additional diseases listed in Table V that cite previous JCA Special Editions containing full fact sheets.

General Considerations

The format of the Special Issue restricts the amount of information which can be provided in each fact sheet. An appendix with information regarding rapidly progressive glomerulonephritis (RPGN) and LDL apheresis device is provided rather than inserting this information into each relevant fact sheet. Textbooks in the field of apheresis medicine which users of the Special Issue may find useful include Apheresis: Principles and Practice, Third Edition [11]. In Table VI, we propose information that may be included in a consultation note before performing an apheresis procedure. This standard approach to consultation may be particularly helpful to readers who may have limited experience in the field of apheresis medicine. An area of potential concern for the apheresis practitioner is the type of replacement fluid to be used during therapeutic apheresis, notably TPE. The reader should be cognizant of the risk of coagulation factor depletion (especially fibrinogen), particularly after daily TPE used in some clinical settings. Plasma supplementation may be considered in these situations. Lastly, issues related to the timing of procedures, such as emergency (treatment indicated 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 and duration of apheresis therapy. This determination should be made using appropriate medical judgment through consultation between the requesting physician and the physician administering apheresis. The 2016 JCA Special Issue should provide useful information to inform practitioners about the evidence-based application of therapeutic apheresis for a wide range of disease states.

GLOSSARY

Therapeutic apheresis procedures considered in this publication and included in the fact sheets are adsorptive cytapheresis, therapeutic plasma exchange (TPE), erythrocytapheresis, red blood cell (RBC) exchange, thrombocytapheresis, leukocytapheresis, filtration-based selective apheresis, extracorporeal photopheresis (ECP), immunoadsorption (IA), LDL apheresis, adsorptive cytapheresis, B_2 microglobulin column, high-volume plasma exchange (HVP), and rheopheresis, defined in Table VII.

APPENDIX

Rapidly Progressive Glomerulonephritis

A number of factsheets in the 2016 JCA Special Issue discuss diseases with rapidly progressive glomerulonephritis (RPGN). RPGN consists of rapid loss of renal function with the histologic finding of crescent formation in more than 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 comprise 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 as follows:

1. Linear deposits of IgG due to autoantibodies to Type IV collagen representing antiglomerular basement membrane (anti-GBM) glomerulonephritis (GN), which 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 poststreptococcal GN, Henoch-Schönlein purpura, IgA nephropathy, membranoproliferative GN, cryoglobulinemia, and lupus nephritis. Immunocomplex RPGN accounts for 24% of cases of RPGN (see fact sheets on Henoch-Schönlein purpura, IgA nephropathy, and systemic lupus erythematosus).
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 polyangitis, 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 (see fact sheet on ANCA-RPGN).

It is important for apheresis medicine practitioners to identify the specific category of RPGN present in their patient as TPE treatment protocols and responses differ among the three categories.

LDL Cholesterol Removal Systems

Six LDL cholesterol removal apheresis systems are available. These include:

1. immunoadsorption columns containing matrix-bound sheep anti-apo-B antibodies;
2. dextran sulfate columns to remove apo-B lipoproteins from plasma by electrostatic interaction;
3. heparin extracorporeal LDL precipitation (HELP) to precipitate apo-B in the presence of heparin and low pH;
4. direct adsorption of lipoprotein using hemoperfusion to remove apo-B lipoproteins from whole blood

through electrostatic interactions with polyacrylate-coated polyacrlyaminde beads;
5. dextran sulfate cellulose columns: same mechanism as (2) above but treats whole blood; and
6. membrane differential filtration to filter LDL from plasma.

Currently, the dextran sulfate plasma adsorption and HELP systems are cleared by the FDA. These multiple removal systems appear to have equivalent cholesterol reduction efficacy. The fact sheets on Familial Hypercholesterolemia and Lipoprotein (a) Hyperlipoproteinemia provide information on LDL cholesterol apheresis as a whole without discussing each system separately.

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ACUTE DISSEMINATED ENCEPHALOMYELITIS

Incidence: 0.4–0.9/100,000/yr[a]	Indication	Procedure	Recommendation	Category
	Steroid refractory	TPE	Grade 2C	II
No. of reported patients: < 100	RCT	CT	CS	CR
	0	0	5(30)	24(29)

[a]In patients <20 years old. In adults, incidence estimates 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. Children and young adults are predominantly affected. The pathogenesis is thought to be disseminated multifocal inflammation and patchy demyelination associated with transient auto-immune response against myelin oligodendrocyte glycoprotein or other autoantigens. It is believed that viral or bacterial epitopes resembling neuronal antigens have the capacity to activate myelin-reactive T cell clones through molecular mimicry, and thus can elicit a central nervous system (CNS) -specific autoimmune response. ADEM typically begins within days to weeks following an infection. 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 with a favorable prognosis. However, recurrent or multiphasic forms have been reported. Death is rare and complete recovery is seen in ~55–95% of cases. MRI is the diagnostic imaging modality of choice for the demyelinating lesions. 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 Cerebrospinal fluid (CSF), predominance of MRI lesions in the subcortical region with relative sparing of the periventricular area, and complete or partial resolution of MRI lesions during convalescence. New lesions should not appear unless a clinical relapse has occurred. A rare hyperacute variant of ADEM, acute hemorrhagic leukoencephalitis, is characterized by a rapidly progressive, fulminant hemorrhagic demyelination of white matter, usually associated with severe morbidity or death.

Current management/treatment

Once ADEM is diagnosed, the therapeutic aim is to abbreviate the CNS inflammatory reaction as quickly as possible, to aid in clinical recovery. There have been no RCTs for the treatment of ADEM, and therapies are based on the analogy of the pathogenesis of ADEM with that of other demyelinating diseases such as MS. High-dose intravenous corticosteroids, such as methylprednisolone 20–30 mg/kg/day (maximum 1 g/day) for 3–5 days is considered as first-line therapy. It may be followed by a prolonged oral prednisolone taper over 3–6 weeks. Corticosteroids are considered effective because of their anti-inflammatory and immunomodulatory effects with additional beneficial effect on cerebral edema. TPE should be considered for patients with severe ADEM, who respond poorly to steroid treatment or in whom it is contraindicated. Additionally, intravenous immunoglobulin (IVIG) has also been used and is typically reserved for patients who are steroid unresponsive.

Rationale for therapeutic apheresis

TPE is thought to work by removing presumed pathogenic autoantibodies in ADEM. A potential candidate target of autoantibodies in ADEM is myelin oligodendrocyte glycoprotein. In one study (Llufriu, 2009) early initiation of TPE (within 15 days of disease onset) in acute attacks of CNS demyelination (including seven 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 on the optimal regimen of TPE in ADEM. In one of the largest ADEM case series (Keegan, 2002), TPE achieved moderate and marked sustained improvement in 50% of the patients. Factors associated with improvement were male gender, preserved reflexes, and early initiation of treatment. In the majority of studies, clinical response was noticeable within days, usually after 2–3 exchanges. In published studies, TPE therapy often consisted of 3–6 treatments.

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ACUTE INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY/GUILLAIN–BARRE SYNDROME

Incidence: 1–2/100,000/yr	Indication	Procedure	Recommendation	Category
	Primary treatment	TPE	Grade 1A	I
	After IVIG[a]	TPE	Grade 2C	III
No. of reported patients > 300	RCT	CT	CS	CR
	19(1770)	0	9(369)	NA
After IVIG[a]	0	0	1(46)	NA

[a]TPE initiated after a course of IVIG at 2 g/kg

Description of the disease

Guillain–Barré syndrome (GBS) consists of a group of neurologic conditions characterized by progressive weakness and diminished/absent myotactic reflexes. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP), which comprise up to 90% of cases of GBS, is an acute progressive paralyzing illness affecting both motor and sensory peripheral nerves. The remainder of GBS cases based upon presenting pathogenic and clinical features are classified as acute motor axonal neuropathy (AMAN), acute motor-sensory axonal neuropathy (AMSAN), Miller Fisher syndrome, and acute autonomic neuropathy. In AIDP, 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 ∼25% of patients. Autonomic dysfunction can cause variability in blood pressure and heart rate. Spontaneous recovery may occur, however neurologic complications persist in up to 20% of patients, with about half of them severely disabled. Mortality is estimated at 3%. Some trials using TPE and/or IVIG in GBS have included AIDP and other variants listed above, while others have included only AIDP. In GBS, an auto-immune pathogenesis is strongly suggested due to the presence of autoantibodies against various gangliosides including GM1, GD1a, GalNAc-GD1a, GD1b, GQ1b, GD3, and GT1a, particularly in AMAN and Miller Fisher syndrome subtypes. Observations of preceding infectious illness, such as Campylobacter, suggest cross-reactive antibodies may be a component in disease pathogenesis.

Current management/treatment

Since spontaneous recovery is anticipated in most patients, supportive care is the mainstay of treatment in ambulatory patients. Severely affected patients may require intensive care, mechanical ventilation, and assistance through 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 RCTs have confirmed its efficacy. An international RCT compared TPE, IVIG, and TPE followed by IVIG in 383 adult patients with severe AIDP and found all three modalities to be equivalent. There were no differences in the three treatment groups in mean disability improvement at 4 weeks nor the time to be able to walk without assistance (TPE group 49 days, IVIG group 51 days, and TPE/IVIG group 40 days). Other therapeutic modalities studied include immunoadsorption apheresis, CSF filtration, and double filtration plasmapheresis. 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 five consecutive days.

Rationale for therapeutic apheresis

The favored etiology of GBS is autoimmune antibody-mediated damage to the peripheral nerve myelin. The results of several controlled trials comparing TPE to supportive care alone indicate that TPE can accelerate motor recovery, decrease time on the ventilator, and speed attainment of other clinical milestones. While recovery with TPE is improved, the duration of disability from AIDP remains significant. For example in the French Cooperative Study, median time to wean from mechanical ventilation was 18 days versus 31 days for TPE compared to conventional treatment, respectively. In the North American Trial, the median time to walk without assistance was 53 days versus 85 days in the TPE and conventional treatment arms, respectively. 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. 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. Evidence-based guidelines of the American Academy of Neurology report equal strength of evidence to support the use of TPE or IVIG in the treatment of GBS, however, the cost of IVIG treatment in GBS may be as high as double the cost of TPE (Winters, 2011).

Retrospective studies suggest that TPE in the setting of IVIG failure has limited therapeutic benefit, and is significantly more expensive. Therefore, requests for TPE after IVIG treatment should be evaluated on a case-by-case basis.

Technical notes

Since autonomic dysfunction may be present, affected patients may be more susceptible to intravascular volume shifts during apheresis treatments. Relapses may occur in up to 5–10% of patients 2–3 weeks following either treatment with TPE or IVIG. When relapses occur, additional TPE is typically helpful.

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

Duration and discontinuation/number of procedures

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 TPE procedures, although some patients may need additional treatments.

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ACUTE LIVER FAILURE

Incidence: $< 10/1,000,000/\text{yr}$		Procedure	Recommendation	Category
		TPE	Grade 2B	III
		TPE-HV	Grade 1A	I
No. of reported patients: > 300	**RCT**	**CT**	**CS**	**CR**
TPE	1(120)	1(158)	40(878)	54(73)
TPE-HV	1(182)	NA	NA	NA

TPE-HV: TPE-High Volume, not available in US.

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 most common causes are acetaminophen toxicity and viral hepatitis. Other known causes include ingestion of hepatotoxins/drugs, autoimmune hepatitis, critical illness, neoplastic infiltration, acute Budd–Chiari syndrome, and heat stroke. 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 $< 20\%$.

Current management/treatment

For ALF with low likelihood of spontaneous recovery, the standard treatment is supportive care as a bridge to liver transplantation. If liver transplantation is not available, other liver support systems have been used. Liver support systems include cell-based and non cell-based therapies. Many of the cell-based liver support systems are considered experimental (Bioartificial liver, Extracorporeal Whole Liver Perfusion, Extracorporeal Liver Assist Device, and Modular Extracorporeal Liver Support). Non-cell-based therapies include: TPE, albumin dialysis, MARS (Molecular Adsorbents Recirculation System: i*n the US, the MARS system is cleared for use in the treatment of drug overdose and poisonings only)*, fractionated plasma separation and adsorption, Single Pass Albumin Dialysis, and Selective Plasma-Exchange Therapy. Other newer promising approaches include hepatocyte transplantation and tissue engineering.

Rationale for therapeutic apheresis

In FHF, TPE can remove albumin bound toxins as well as unbound 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. Recent studies indicate that the removal of inflammatory mediators appears to play a role and inflammatory mediators are removed by some apheresis techniques. Several studies show improved cerebral blood flow, mean arterial pressure (MAP), 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. One study found that TPE does not reduce vasopressor requirement, despite positive changes in MAPs. 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 the period of TPE treatment and in other patients, failure may persist necessitating liver transplantation. Aggressive TPE has been used as a bridge to liver transplantation. When it is indicated, TPE is often performed emergently in this setting.

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. Similarly, Li (2014) reported that the combined use of TPE, hemoperfusion (HP), and conventional continuous veno-venous hemofiltration removed toxic metabolites, especially bilirubin more efficiently than other combination without TPE. A controlled trial by Yue-Meng (2016) showed significant survival benefit in patients who received TPE versus those who did not for patients with entecavir-treated hepatitis B and hepatic de-compensation or acute-on-chronic liver failure. The cumulative survival rates were 37% (TPE) and 18% (non TPE) at week 4 and 29% (TPE) and 14% (non TPE) at week 12 ($P < 0.001$). In Denmark, TPE-high volume (TPE-HV, often performed with PrismaFlex-TPE filter system, Gambro) has been used to treat ALF. A recent RCT (Larsen, 2016) performed in 183 patients demonstrate statistically significant overall survival benefit: 58.7% TPE-HV + standard care versus 47.8% standard care ($P < 0.001$) when three daily procedures were targeted.

Technical notes

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

Volume treated: TPE: 1–1.5 TPV; TPE-HV: target 15% of ideal body weight	**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 TPE would be expected to appear better compared to pre-TPE levels. The TPE-HV was performed on three consecutive days.

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AGE-RELATED MACULAR DEGENERATION, DRY

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

No. of reported patients: > 300	RCT	CT	CS	CR
	8(490)	2(359)	8(97)	NA

Description of the disease

Age-related macular degeneration (AMD) is the leading cause of blindness among the elderly in developed countries. It is a progressive condition resulting in central vision loss. "Dry" AMD is the most common form and is characterized by the development of collections of debris (drusen) which disrupt retinal function and may progress to geographic atrophy leading to loss of vision over time. "Wet" AMD, the most severe form of the disease, is characterized by abnormal macular neovascularization. Environmental risk factors for AMD include smoking and obesity. Genetic risk factors include mutations in complement, cholesterol, collagen matrix, and angiogenesis pathways. The pathogenesis of AMD has not been completely elucidated but senescence, characterized by lipofuscin accumulation in retinal pigment cells, choroidal ischemia, and oxidative damage may play a role.

Current management/treatment

Medical management of dry AMD is limited to oral supplements containing high doses of antioxidants and zinc. A variety of targeted therapies are in development and include agents that decrease oxidative stress, suppress inflammation, reduce toxic by-products, or function as visual cycle modulators, neuroprotectants, or vascular enhancers. Wet AMD is currently treated with laser photocoagulation, photodynamic therapy, and anti-vascular endothelial growth factor therapy.

Rationale for therapeutic apheresis

Rheopheresis (also called double filtration plasmapheresis, cascade filtration plasmapheresis, or double membrane plasmapheresis) removes high-molecular weight molecules (e.g., fibrinogen, LDL-cholesterol, fibronectin, von Willebrand factor) which may impair the retinal microcirculation or contribute to a chronic inflammatory state. Rheopheresis also results in a reduction in blood and plasma viscosity, platelet and red cell aggregation, and enhanced red cell membrane flexibility which may also improve retinal pigment epithelium (RPE) perfusion and function.

Multiple studies have reported the efficacy of rheopheresis in the treatment of dry AMD. The most recently published randomized controlled trial of rheopheresis for dry AMD studied 38 patients randomized to receive 8 procedures over 10 weeks and compared them to 34 control patients not treated by rheopheresis. They found that the best-corrected visual acuity increased significantly from 0.61 (0.06–1.00) to 0.68 (0.35–1.00) in the treatment group ($P = 0.035$) (Blaha, 2013). The same group also noted significant reduction in the drusenoid retinal pigment epithelium detachment area in a controlled trial of 25 patients (Rencova, 2013). Both studies showed no progression to wet AMD in the treatment group during the 2.5-year follow-up period, suggesting that rheopheresis may slow or stop the progression of dry AMD.

The largest controlled trial to date is from the RheoNet registry (Klingel, 2010). 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 line on Early Treatment Diabetic Retinopathy Study (ETDRS) charts 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 versus 40% of controls. These were statistically significant differences.

The MIRA-1 trial, the largest randomized double-blinded placebo (sham procedure) controlled trial to date, enrolled 216 patients yet 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 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 (Pulido, 2006).

Criticism of current evidence supporting the use of rheopheresis for treatment of dry AMD includes the lack of understanding regarding the mechanism by which removal of high molecular weight plasma components improves the RPE microcirculation, uncertainty surrounding the clinical relevance of reported visual improvements and the natural history of the disease which may have a stable course without deterioration for long periods of time and drusen which may spontaneously regress and disappear without treatment (Finger, 2010).

Technical notes

The majority of series and trials used double filtration plasmapheresis where plasma is first separated by centrifugation and then passed through a rheofilter where high-molecular weight substances are removed. Currently, the filtration devices necessary for this treatment are not licensed in the US but are available in Europe and Canada.

Volume treated: 0.8–1.5 TPV	Frequency: 8–10 treatments (2/wk) over 8–21 wk
Replacement fluid: NA	

Duration and discontinuation/number of procedures

Efficacy of a single course of treatment has been reported to last for up to 4 years.

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AMYLOIDOSIS, SYSTEMIC

Incidence: Primary AL amyloidosis: 6–10/1,000,000/yr; 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
	β_2-microglobulin column	Grade 2B	II
	TPE	Grade 2C	IV

No. of reported patients: >300	RCT	CT	CS	CR
β_2 microglobulin column	1(36)	1(17)	2(412)	NA
TPE	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 heterogeneous group of genetic and acquired disorders characterized by pathological extracellular deposition of insoluble polymeric fibrils consisting of misfolded proteins or protein precursors, 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 β_2-microglobulin (dialysis-related amyloidosis [DRA]). AL amyloidosis, associated with multiple myeloma, Waldenström's 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 and 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. The goal of treatment for primary systemic AL amyloidosis is eradication of the underlying plasma cell disorder, thus the same chemotherapy regimens, targeted agents, and autologous hematopoietic stem cell transplantation (HSCT) approaches are used. End-organ complications are managed with symptomatic and supportive care. Management of coagulopathy 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. Recently, there is promising data in the use of targeted therapy aimed at reducing amyloid deposits in tissues. In a randomized Phase II clinical trial, eprosidate was shown to slow the progression of kidney disease in patients with AA amyloidosis. A Phase III trial is currently underway. DRA can be managed with aggressive dialysis using membranes and treatment protocols that optimize clearance of β_2-microglobulin; however, kidney transplantation is the treatment of choice. Bone and joint complications of DRA are managed symptomatically. No agents are yet approved that directly solubilize the amyloid that deposits in affected tissues.

Rationale for therapeutic apheresis

Case reports and small case series have described the use of intensive TPE with immunosuppressive treatment to manage rapidly progressive glomerulonephritis (RPGN) with AA amyloidosis. In one report, regular TPE treatments over 8 months 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 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. Specialized adsorption columns or membrane filters to remove β_2-microglobulin have been used extensively in Japan for dialysis-related amyloidosis. A randomized controlled trial of 36 patients demonstrated a significant improvement in activities of daily living (ADL), stiffness, and pain scores in the β_2-microglobulin column group ($n = 18$) after two years. In a study of 17 patients, each acting as their own control, pinch strength and ADL scores were improved after one year of treatment. More recently, a survey of 138 institutions revealed that attending physicians considered β_2-microglobulin adsorption column treatment to be at least partially effective in greater than 70% of patients ($n = 345$ patients).

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ANCA-ASSOCIATED RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (GRANULOMATOSIS WITH POLYANGIITIS AND MICROSCOPIC POLYANGIITIS)

Incidence: 8.5/1,000,000/yr	Indication	Procedure	Recommendation	Category
	Dialysis dependence[a]	TPE	Grade 1A	I
	DAH	TPE	Grade 1C	I
	Dialysis independence[a]	TPE	Grade 2C	III
No. of reported patients: > 300	RCT	CT	CS	CR
	8(296)	1(26)	22(347)	NA

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

Description of the disease

GPA (or Wegener's) and MPA, also known as ANCA-associated vasculitis and ANCA-associated pauci-immune rapidly progressive glomerulonephritis (RPGN), are major causes of RPGN (see Appendix) and can be associated with DAH occasionally. There is rapid loss of renal function with the histologic finding of crescent formation in over 50% of glomeruli. These crescents represent proliferation of cells within Bowman's space of the glomerulus due to proteinextravasation into this space. These cells comprise proliferating parietal epithelial cells and infiltrating macrophages and monocytes. ANCA-associated RPGN is usually associated with minimal immune deposits in the glomerulus and ANCA positivity (either c-ANCA or p-ANCA). GPA, more often associated with c-ANCA, and MPA, more often associated with p-ANCA, are related systemic vasculitidies, with ANCA positivity and similar outcomes.

The presentation of the pulmonary-renal syndrome associated with ANCA can be clinically similar to anti-glomerular basement membrane (GBM) disease (Goodpasture's Syndrome). DAH associated with ANCA vasculitis poses significant mortality risk. When ANCA and anti-GBM are both present, the disease should be considered to represent anti-GBM disease (see anti-GBM disease fact sheet).

Current management/treatment

Without treatment, GPA/MPA frequently progresses to ESRD over months. Symptoms include malaise, intermittent fever, weight loss, respiratory distress, and diffuse pain in joints and can culminate in mortality. The current management is combination therapy consisting of high-dose corticosteroids and cytotoxic immunosuppressive drugs (cyclophosphamide and rituximab). 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, mycophenolate mofetil, and antibodies against T-cells. Overall, existing controlled trials suggest no benefit of TPE for many cases with kidney involvement. Important exceptions are: Patients with (1) severe active kidney disease, i.e., 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

The presence of ANCA autoantibodies indicates a humoral component in 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 exclusively GPA/MPA, which complicates data interpretation. Compared to the benefit of TPE in RPGN caused by anti-GBM, the benefit in type II (immune-complex) or III (GPA/MPA) RPGN is less certain. Six trials have examined the TPE in ANCA and immune-complex GNs. Of these, three 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 with less severe acute kidney injury. Another trial consisting of 14 patients found benefit in all. Overall, 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 prospective study of 137 patients presenting with an initial diagnosis of 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/day × 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%). TPE was also a positive predictor of recovery for those already on dialysis. High mortality (roughly 25%) occurred in both groups at one year. 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. Some more recent long-term (more than 10 years) outcome studies show that the short-term improved outcome in the TPE group may not be sustained long-term. A multicenter international RCT is in progress to ascertain the efficacy of TPE plus immunosuppressive therapy and glucocorticoids at reducing death and ESRD in ANCA positive vasculitis (PEXIVAS). RCTs of TPE in patients with RPGN and DAH have not been conducted. However, retrospective case series reported effective management of DAH in GPA/MPA.

Technical notes

In patients with DAH, replacement with plasma is recommended to avoid dilutional coagulopathy.

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 DAH then every 2–3 days for total of 6–9 procedures.

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

Incidence: 1/1,000,000/yr	Indication	Procedure	Recommendation	Category
	Dialysis-dependence[a], no DAH	TPE	Grade 2B	III
	DAH	TPE	Grade 1C	I
	Dialysis-independence[a]	TPE	Grade 1B	I
No. of reported patients: > 300	RCT	CT	CS	CR
	1(17)	0	19(468)	21

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

Description of the disease

Goodpasture's syndrome (GS) is a rare and organ-specific autoimmune disease. It is mediated by anti-glomerular basement membrane (anti-GBM) antibodies directed against a domain of $\alpha 3$ chain of Type IV collagen, causing activation of the complement cascade, resulting in tissue injury due to a classic Type II reaction. Only alveolar and GBM are affected, therefore, symptoms include crescentic or rapidly progressive glomerulonephritis (RPGN) and diffuse alveolar hemorrhage (DAH). Up to 30–40% of patients have been reported to have only renal limited involvement. Pulmonary symptoms range from breathlessness to overt hemoptysis. Chest radiography is a useful tool in demonstrating DAH but findings are nonspecific. Anti-GBM is associated with a specific HLA allele, DRB1*1501. Almost all patients have anti-GBM antibodies detectable in their blood. Also, 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. GS affects more Caucasians than African Americans with a bimodal age distribution, 20–30 years and 60–70 years. GS has important differential diagnosis including Wegener granulomatosis, systemic lupus erythematosus, microscopic polyangiitis, other systemic vasculitis, and connective tissue diseases. Without treatment GS is a life threatening disease. It is important to identify the specific RPGN category in their patient as TPE treatment protocols and responses differ. Prognosis of GS is strongly correlated to an early treatment. The three principles are to rapidly remove circulating antibody, to stop further production of antibodies, and to remove offending agents (hydrocarbon fumes, metallic dust, tobacco smoke, infections [influenza A], cocaine, etc).

Current management/treatment

In GS, treatment includes the combination of TPE, cyclophosphamide, and corticosteroids. In general, the disease does not relapse in a successfully treated patient and therefore such patients do not require chronic immunosuppression. The exception is patients with ANCA and 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 transplanted allograft 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 > 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. IA and DFPP have been used in few cases with efficient removal of anti-GBM antibodies. DAH can be rapidly fatal, or 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 knowledge that the disorder was associated with the presence of autoantibodies and the poor prognosis with treatments available at the time (90% would either die or require long-term hemodialysis), TPE was applied for treatment of this disorder in the early 1970s. 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 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 this disorder, treat protocols are the same as adults, but there are limited data concerning outcome in this. Of note, some studies have found that patients with DAH but no renal involvement do well irrespective of the use of TPE.

Technical notes

In the setting of DAH, plasma should be used for part or whole of the replacement fluid.

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; thus, the minimum course of TPE should be 10–20 days. The presence or absence of antibody 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.

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APLASTIC ANEMIA; PURE RED CELL APLASIA

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

No. of reported patients: < 100	RCT	CT	CS	CR
AA	0	0	2(6)	5(5)
PRCA	0	0	2(7)	21(29)

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 disorders. AA is defined by pancytopenia/reticulocytopenia and a hypocellular bone marrow in the absence of neoplastic hematopoiesis, abnormal cellular infiltration, or increased reticulin fibrosis. PRCA is characterized by normochromic, normocytic anemia, reticulocytopenia, 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 idiopathic or secondary to malignancy, thymoma, autoimmune or infectious diseases, certain drugs, and chemicals. Acquired AA (aAA), mostly idiopathic, is to immune-mediated destruction of hematopoietic stem and progenitor cells (HSPC). Dysregulated T cell responses, shortened telomeres, and somatic mutations in myeloid malignancy-related genes, and elevated inflammatory cytokines have been demonstrated in aAA patients.

Acquired PRCA (aPRCA) may result from immune-mediated injury of erythroid progenitors by IgG antibodies, cytotoxic T lymphocytes, and/or their soluble inhibitory or proapoptotic cytokines. Over 200 cases of aPRCA have been reported in patients treated with recombinant human erythropoietin formulations that induced anti-erythropoietin antibodies. aPRCA occurs as a post-transplant complication in 8–26% of major ABO mismatched allogeneic hematopoietic stem cell transplantation (HSCT) patients (see HSCT, ABO incompatible fact sheet). aPRCA may present at any age with symptoms of severe hyporegenerative anemia. aAA occurs most commonly between 15 and 25 years with a second smaller peak > 60 years. aAA symptoms occur 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) < 0.5×10^9/L, platelet count < 20×10^9/L or reticulocyte < 40×10^9/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 identified 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. Matched-related HSCT is the preferred treatment for severe AA in patients <40 years with long-term survival rates > 70% and > 90% of patients <20 years are cured. Similar survival is reported for HLA-matched unrelated HSCT in children and younger adults without a sibling donor; however, morbidity is greater because of higher rates of graft-versus-host disease and therefore non-transplant therapies are often preferred. 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 A. Hematopoietic growth factors and androgens are sometimes used as adjunctive therapies. The response rate to immunosuppressive therapy, with recovery to normal or adequate blood counts, is 60–70%. aPRCA is also usually responsive to immunosuppressive therapy. Corticosteroids alone yield a 40% response rate. If no response is achieved after 2–3 months of primary immunosuppressive 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-related HSCT has been used for selected cases of refractory PRCA. Matched HSCT should also be considered for older patients with refractory severe AA. For younger patients with refractory AA and no matched donor, cord blood HSCT 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

A variety of autoantibodies have been identified in patients with AA. TPE may be helpful by removing these autoantibodies 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 therapeutic option for selected patients; especially those who are unresponsive to conventional immunosuppressive therapies and when there is no HSCT option. TPE may also improve post-transplant PRCA in the setting of a major ABO-mismatched donor by removing persistent host isoagglutinins and in the setting of erythropoietin-induced PRCA 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.

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ATOPIC (NEURO-) DERMATITIS (ATOPIC EZCEMA), RECALCITRANT

Incidence: Children: atopic dermatitis 10–30%; adults: 1–3%; recalcitrant: rare		Procedure	Recommendation	Category
		ECP	Grade 2C	III
		IA	Grade 2C	III
		TPE	Grade 2C	III

No. of reported patients: 100–300	RCT	CT	CS	CR
ECP	0	0	9(104)	1(1)
DFPP	0	1(9)	0	0
IA	0	0	3(19)	0

Description of the disease

Atopic dermatitis (AD), or eczema, is the most common chronic relapsing skin disease seen in infancy and childhood. It affects 10–30% of children worldwide and frequently occurs in families with other atopic diseases. Infants with AD are predisposed to development for allergic rhinitis and/or asthma later in childhood, a process called "atopic march." AD is a complex genetic disorder that results in a defective skin barrier, reduced skin innate immune responses, and exaggerated T-cell responses to environmental allergens and microbes that lead to chronic skin inflammation. Persistent skin inflammation may be associated with a relative lack of T-regulatory cells in the skin. AD is characterized by T-cell dysfunction, hypereosinophilia, and high levels of IgE. The latter is due to an induce isotype switching to IgE synthesis by the CLA+ T-cells (CLA = cutaneous lymphocyte-associated antigen). IgE measurements or prick tests can identify allergens to which the patient is sensitized. AD often goes into remission as the patient grows older, leaving an adolescent or adult with skin prone to itching and inflammation when exposed to exogenous irritants, but however few individuals have life-long AD with severe symptoms.

Current management/treatment

The treatment of AD requires a systematic, multifaceted approach that incorporates skin hydration, topical anti-inflammatory therapy (including tacrolimus), identification, and elimination of flare factors (especially foods), and, if necessary, systemic therapy. In refractory disease phototherapy (UVA-1, UVB, or PUVA) are used. Treatments for third-line or under investigation are interferon-γ, omalizumab, allergen immunotherapy, probiotics, Chinese herbal medications, and antimetabolites. Important for clinical studies is the use of valid clinical scoring system. In AD the SCORAD (SCORing Atopic Dermatitis) is widely used for evaluating the treatment success.

Rationale for therapeutic apheresis

ECP: Given the side effects of third-line therapies including immunosuppressive agents and phototherapies ECP is used as a non-toxic and non-immunosuppressive alternative third-line therapy. Since 1994 105 cases have been published with a 70% of patients having a favorable response to ECP, requiring at least six cycles for a response. The following recommendations were published: ECP may be considered in a patient with AD who fulfils the following criteria: a diagnosis of severe AD of at least 12 months duration, SCORAD > 45, resistance in the last 12 months to all first-line therapies used to treat AD, including topical steroids, topical calcineurin inhibitors, and one form of phototherapy or resistance to either systemic steroids or cyclosporine as second-line therapy.

TPE and DFPP: TPE and DFPP are used to reduce IgE and immune complexes from patients' blood. For DFPP there is one controlled trial showing a significant improvement.

IA: IA is able to reduce significant level of IgE. Both non-specific and IgE-specific columns have been used. Of note, only a short-term decrease of the serum IgE, followed by fast recovery of IgE levels within 3 weeks after discontinuation of IA, was observed, whereas the skin-bound IgE in the dermis and epidermis (proved by biopsies) was reduced until the end of the observation period, 13 weeks after the initial IA. In parallel, decreased skin infiltration by inflammatory cells and improved skin architecture were observed.

Technical notes

Volume treated: ECP: Typically, MNCs are obtained from processing 1.5L of whole blood, but the volume processed may vary based on patient weight and HCT. The 2-process method collects and treats MNCs obtained from processing 2 TBV. TPE and DFPP: 1–2 TPV; IA: 2–4 TPV

Replacement fluid: Albumin

Frequency: ECP: 1 cycle every 2 weeks for 12 weeks, then tapering; TPE and DFPP: weekly; IA: series of up to 5 consecutive daily IA every 4 weeks

Duration and discontinuation/number of procedures

The initial ECP treatment for AD should be one cycle (2 treatments) every 2 weeks for 12 weeks, thereafter ECP treatment should be given depending on individual response every 3–4 weeks, and then tapered to every 6–12 weeks before stopping. Relapse could be treated by returning to the interval frequency of the previously effective treatment schedule.

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AUTOIMMUNE HEMOLYTIC ANEMIA, SEVERE

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

No. of reported patients: < 100	RCT	CT	CS	CR
WAIHA	0	0	3(14)	27(30)
CAD	0	0	2(6)	25(26)

WAIA = warm autoimmune hemolytic anemia; CAD = cold agglutinin disease.

Description of the disease

Autoimmune hemolytic anemia (AIHA) represents a group of disorders in which autoantibodies mediate either intravascular hemolysis 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 hemolysis (anemia, hyperbilirubinemia, elevated serum LDH) with a positive direct antiglobulin (Coomb's) test (DAT). 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 RBC antigens. Causes of WAIHA include: idiopathic (30% of cases), secondary (associated with underlying autoimmune diseases, lymphoproliferative disorders, infections, or after HSCT/solid organ transplantation) and drug-induced (e.g., methyl-dopa, cephalosporins, and tacrolimus)). In WAIHA, the DAT is positive with anti-IgG and potentially anti-C3b. CAD results from IgM autoantibodies that react optimally at 0–5°C and may be directed against the 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 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 been described. In CAD, the DAT is positive with anti-C3b only. The severity of hemolysis in AIHA may be influenced by the autoantibody titer, avidity to relevant RBC antigens, ability to fix complement, and, for cold autoantibodies, most importantly 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.

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 hemolysis in the spleen. Splenectomy, despite being underutilized, is perhaps the most effective and best-evaluated second-line therapy, but there are only limited data on long-term efficacy. Rituximab is another second-line therapy with documented short-term efficacy, and limited information on long-term efficacy. Other modalities used in refractory cases include IVIG, cyclophosphamide, vincristine, azathioprine, switching immunosuppression regimen from calcineurin to mTOR inhibitor based, and newer monoclonal antibodies such as alemtuzumab.

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 and is now recommended first-line therapy, although complete and sustained remissions are uncommon. In a recent prospective study (Berentsen, 2004), 20 of 27 patients with CAD responded to rituximab treatment. Prednisone is usually ineffective, as is splenectomy, because the liver is the dominant site of destruction of C3b-sensitized RBCs. Recently, newer drugs such as eculizumab and bortezomib have also shown promise. 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. In WAIHA, several case reports/series have shown favorable results with the use of TPE. However others demonstrate no effect. In one case series utilizing TPE in the setting of severe WAIHA, TPE versus no TPE did not demonstrate differences in increase in hemoglobin levels post-transfusion. A recent retrospective study reported on the use of whole blood exchange (WBE) (Li, 2015) for severe AIHA. IgM autoantibodies in CAD are primarily intravascular and thus might effectively be removed by TPE. In addition, TPE might be beneficial in patients with CAD before surgery which would require hypothermia (Barbara, 2013). 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, RBC 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 TPV	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.

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BABESIOSIS

Incidence: 1,124 cases in the US in 2011; endemic in northeast and great lakes regions	Indication	Procedure	Recommendation	Category
	Severe	RBC exchange	Grade 2C	II
No. of reported patients: < 100	RCT	CT	CS	CR
	0	0	3(14)	15(16)

Description of the disease
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*, *B. venatorum*, and M01-type *B sp*. 95% of cases in the US are in CT, MA MI, NJ, NY, RI, and WI, but cases have been reported in almost every state.

The disease is usually transmitted from an animal reservoir to humans by the bites of *Ixodes* ticks, usually between May through October. Babesiosis can be also transmitted by blood products, mostly RBCs from asymptomatic blood donors, and transmitted vertically. The incubation period is usually 1–3 weeks, with longer incubation period (usually 6–9 weeks) reported with transfusion transmission.

Three types of distinct presentations have been described: (1) Asymptomatic infection which can persist for months–years. Although the CT seroprevalence is 0.3–17.8%, the number of reported cases is 44 per 100,000 based on CMS report. (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. Patients commonly have thrombocytopenia and anemia. The illness usually lasts weeks–months, occasionally with prolonged recovery lasting > year with or without treatment. (3) Severe disease which generally occurs in people with underlying immunosuppressive conditions including HIV, malignancy, immunosuppressive medication, and after splenectomy. Other risk factors include: age ≥50 and simultaneous infection with Lyme disease. Symptoms in severe disease include acute respiratory failure, disseminated intravascular coagulopathy (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 (all-cause mortality <1% of clinical cases and about 10% in transfusion transmitted cases).

Diagnosis is through microscopic identification of the organism using Giemsa-stained thin blood smear, PCR, and/or serologic testing. The detection of IgM is indicative of recent infection while IgG titer of 1:1,024 or greater usually signify active or recent infection. About 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–moderate disease includes antibiotics. Most people can be successfully treated with atovaquone and azithromycin administered for 7–10 days. Combination of quinine sulfate and clindamycin is equally effective but associated with more adverse reactions. In severe disease, treatment usually is quinine sulfate and clindamycin for 7–10 days. 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 with ongoing monitoring.

Rationale for therapeutic apheresis
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 infected RBCs and replacing them with non-infected RBCs. 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, removal of cytokines produced by the hemolytic process, including INF-γ, TNF-α, IL-1, IL-6, nitric oxide, and thromboplastin substances, which can promote renal failure and DIC. The greatest advantage of RBC exchange over antibiotic therapy is its rapid therapeutic effectiveness. In severe cases, the benefits may 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 post-procedure Hct, fraction of RBCs remaining and, by inference, the estimated final parasite load. A 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 unclear. 10% 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 unclear. Treatment is usually discontinued after achieving <5% residual parasitemia. Decision to repeat the exchange is based on the level of parasitemia post-exchange as well as the clinical condition (ongoing signs and symptoms).

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BURN SHOCK RESUSCITATION

Incidence: 50,000 admissions for burn injuries/yr		Procedure TPE	Recommendation Grade 2B	Category III
No. of reported patients: 100 – 300	RCT 1(17)	CT 2(66)	CS 6(102)	CR 0

Description of the disease

Major thermal injury involving $> 25\%$ total body surface area (TBSA) results in clinically significant, potentially fatal physiologic consequences. Increased capillary permeability and intravascular volume deficits predispose to cellular shock releasing inflammatory mediators due to diminished organ perfusion. Disruption of the sodium–potassium membrane pump results in an intracellular sodium shift contributing to 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. Acute respiratory distress (ARDS) may occur from inhalational injury or excessive edema. Life threatening infections occur due to suppressed leukocyte chemotactic function, lymphocyte suppression, and loss of skin barrier.

Current management/treatment

The treatment in the immediate post-burn period is aggressive intravenous fluid resuscitation with crystalloid. American Burn Association practice guidelines indicate that the volume of fluid resuscitation is 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 resuscitation delay may have greater fluid requirements.

Rationale for therapeutic apheresis

The theoretical benefit to TPE in the setting of acute burn shock is based on removing circulating factors such as inflammatory mediators or other humoral substances participating in major burn pathophysiology. Replacement with plasma may decrease in capillary permeability, and improve intravascular oncotic pressure, which might improve response to fluid resuscitation, improve mean arterial pressure (MAP), increase UOP, and immune function.

In the only reported RCT of TPE in burn resuscitation (Kravitz, 1989), TPE did not alter the course of burn shock in 17 patients (9 TPE, 8 control arm). However, mean full-thickness burn injury was significantly higher in the TPE group, completion of resuscitation was accomplished earlier. There were three deaths in the TPE group versus none in the control group. A retrospective historic controlled trial of 40 patients 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. 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, 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 case series of 37 patients 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 RCTs is needed to establish the efficacy and safety of TPE. The American Burn Association acknowledges that TPE is sometimes applied empirically as a salvage therapy; it has identified the use of TPE in burn resuscitation as an area for research because of the lack of Level 1 evidence (Gibran, 2013).

Technical notes

TPE was instituted early in the post-burn 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 $1.2\times$ the volume predicted by the modified Baxter formula (3 cm^3 LR/kg/%TBSA) to be necessary to keep UOP >50 cm^3/h and/or MAP ≥ 65 mmHg. The choice of replacement fluid is dependent on the indication for TPE, concomitant infection, and bleeding risk.

Volume treated: 1.5 TPV	**Frequency**: Once, see below
Replacement fluid: Albumin, plasma	

Duration and discontinuation/number of procedures

TPE typically performed within the first 24 h (8–16 h) with additional 1 or 2 TPE procedures in selected patients whose MAP and UOP did not increase or whose IV fluid volumes did not decline to predicted volumes (second TPE within 6–8 h of first).

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CARDIAC NEONATAL LUPUS

Incidence: 2% of anti-SSA positive mothers		Procedure TPE	Recommendation Grade 2C	Category III
No. of reported patients: < 100	**RCT** 0	**CT** 0	**CS** 4(20)	**CR** 13(15)

Description of the disease

Congenital lupus can result in dermatologic, hematologic, hepatic, musculoskeletal, and CNS manifestations. Congenital lupus affecting the cardiovascular system can result in congenital heart block (CHB) and cardiomyopathy. CHB is an acquired immune-mediated disease caused by placental transfer of maternal antibodies beginning at 12 week gestational age (GA). Most commonly anti-Ro (anti-SSA [Sjögren syndrome-A]) alone, or in combination with anti-La (anti-SSB [Sjögren syndrome-B]), or anti-ribonuclear protein antigens [RNP] antibodies are the cause. The antibodies damage fetal cardiac conduction system, causing inflammation and fibrosis, leading to blockage of signal conduction through the atrioventricular (AV) node leading to heart block predominantly between 18 and 24 week GA, but can occur throughout the pregnancy. Anti-SSA/SSB cross react with calcium channels in the myocardium resulting in inflammation and fibrosis, leading to endocardial fibroelastosis (EFE) and progression to heart failure, hydrops fetalis, and potentially death.

Two percent of mothers positive for anti-SSA and 1% of mothers with SLE have children with CHB. Mothers may be asymptomatic (22–40% asymptomatic; 50% develop autoimmune symptoms later) or have SLE, Sjögren syndrome, antiphospholipid syndrome, or other autoimmune tissue disorders. Forty-one percent (41%) of neonates have at least one other affected sibling; there is a 17% chance of recurrence in subsequent pregnancies. Genetics and environment appear to play a role in disease manifestation: fraternal twins may not both demonstrate CHB and incidence is higher in winter. With 2nd or 3rd degree AV block, 91% survive birth, 93% of the survivors live through the neonatal period, and 2/3 require pacemaker by 1 year. Death is associated with earlier onset of disease (GA<20 week), ventricular rate ≤ 50 bpm, fetal hydrops, and impaired left ventricular function. Fetal/neonatal mortality is higher in non-whites and older maternal age. Prenatal diagnosis is made by fetal echocardiogram which demonstrates varying degrees of CHB and diffuse thickening of endocardium with or without ventricular dysfunction or hydrops. Postnatally, neonates can present with clinical manifestation of the skin, persistent neonatal bradycardia with electrocardiogram consistent with CHB, or only with electrocardiogram changes.

Current management

The current recommendation is for pregnant women with positive SSA $\pm$ SSB antibodies to have fetal cardiac evaluation every 2–3 week from 18 to 28 wk GA to evaluate cardiac rhythm and function. Treatment is either prophylactic, when a mother has had a previously affected fetus/neonate, or as treatment when CHB is detected. The mainstay of maternal treatment is fluorinated steroids and β-agonists; adjuvant therapies include TPE, IVIG, hydroxychloroquine, and other immunosuppressive agents. Recent study demonstrate that initiation of maternal hydrochloroquine therapy prior to 10 week GA in women with anti-SSA or SSB and previously affected child may decrease CHB in current pregnancy. IVIG has been found to lower titers of the causative antibody by 80%, although mothers with high Id:anti-Id ratio had no effect on prevention. The Preventive IVIG Therapy for Congenital heart Block (PITCH) study enrolled 20 mothers, who were given low-dose IVIG (400 mg/kg every 3 week) starting at 12–24 week GA, which did not prevent recurrence.

Treatment of the mother for fetal reversal of 3rd degree CHB has not been achieved, but it has been stabilized. 1st or 2nd degree CHB can be reverted to normal sinus rhythm in some studies.

Rationale for therapeutic apheresis

Since CHB is caused by antibodies, removal of the antibodies by TPE may potentially prevent or reverse the disease. Multiple case series and reports have been published with varying success and regimens. TPE regimens varied from 3 per week, weekly, every other week, to monthly. All patients received steroids and, if for treatment, also often received IVIG or azathriopine. In three patients with anti-SSA and mild fetal cardiac involvement who received IVIG, TPE, and steroids, fetal disease was halted and none required a pacemaker (Martinez-Sanchez, 2015). Another CS of 6 patients (3 with 2nd CHB and 3 with 3rd CHB), describes a regimen of TPE given two consecutive days then weekly until delivery, consisting of 70–100% volume exchange with 4% albumin; betamethasone (4 mg/day) then prednisone taper postpartum; and IVIG pre- and post-delivery (1 g/kg/day) at 15-day intervals; and low dose aspirin (Ruffatti, 2013). The fetuses with 2nd degree CHB reverted to normal conduction while those with 3rd degree CHB remained stable or improved. This group used a similar regimen for 2 previous (successful reversion of 2nd degree) and 4 future (no reversion of 2nd or 3rd degree) pregnancies. In those pregnancies that responded, antibody titers fell long-term. A single case series of four patients using IA has been reported, which demonstrated prevention but not treatment of disease.

Technical notes

One case had small placental hemorrhage which could have been due to anticoagulation during and after TPE.

Volume treated: 1 TPV	**Frequency**: 3/week to weekly to monthly
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

TPE regimens varied substantially. Some only treated until antibody levels decreased and stayed low.

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CARDIAC TRANSPLANTATION

Incidence: ~2,300 transplants performed per year in the US; Rejection prophylaxis: Infrequent; Cellular rejection: 21–30% in 1st post-transplant yr; Desensitization/AMR rates: Unknown	Indication	Procedure	Recommendation	Category
	Cellular/recurrent rejection	ECP	Grade 1B	II
	Rejection prophylaxis	ECP	Grade 2A	II
	Desensitization	TPE	Grade 1C	II
	AMR	TPE	Grade 2C	III

No. of reported patients: ECP: >300; TPE: >300	RCT	CT	CS	CR
Rejection prophylaxis	1(60)	2(38)	1(2)	0
Cellular rejection	0	0	4(58)	2(4)
Desensitization	0	4(76)	8(124)	2(2)
AMR	0	0	>10(>199)	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 medicated (AMR), acute cellular rejection (ACR) (most commonly), or chronic rejection (allograft vasculopathy). ACR is mediated through T cells. AMR is mediated by antibodies directed to the allograft and is more likely to cause hemodynamic instability, or may manifest as decreased ejection fraction. AMR has a poorer prognosis than ACR and is highly associated with the early development of allograft vasculopathy. Young age, female, history of congenital heart disease, high titer of HLA antibodies, positive pretransplant crossmatch, sensitization to OKT3, or prior cytomegalovirus exposure increases the risk of AMR.

Current management/treatment

Rejection is treated by immunosuppression. Steroids are used for episodes of rejection. If AMR progresses, rituximab and TPE are considered. Because many past studies focusing on desensitization were performed with older medical regimens, they should be assessed with consideration for newer agents, such as bortezomib.

ECP has been promoted to improve outcome after recalcitrant/severe rejection. In the largest adult study, ECP treatment in 36 patients decreased rejection significantly (Kirklin, 2006). The hazard for subsequent rejection or death was significantly reduced toward the level of the lower-risk non-ECP treated patients in the study. In a RCT comparing ECP vs. non-ECP in the prevention of rejection (Barr, 1998), after six months, 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 first episode of rejection, incidence of hemodynamic compromise, or survival at 6 and 12 months. In pediatrics, a 20 patient retrospective cohort found decreased number of rejection episodes in 6 months after ECP compared to 6 months before initiation of therapy (1.5 vs. 0.5, $P = 0.002$). Protocols for measuring response to ECP include Tregs, plasmacytoid dendritic cells, and cytokine levels, which have been found to be altered by ECP. A consensus conference report on the sensitized patient awaiting heart transplantation discusses several aspects of this process (Colvin, 2015). Several programs treated patients with pre-transplant PRAs >50% and typically use combination of TPE, IVIG, and rituximab. In a 21 patient retrospective review, HLA antibodies were decreased from PRA 70.5% to 30.2%, which resulted in being able to proceed to transplant with similar 5-year survival and freedom from vasculopathy compared to sensitized patients that did not get treated and non-sensitized patients.

All studies using TPE for AMR have been observational and retrospective in nature. The identification of pathogenic donor specific HLA antibodies includes use of the C1q assay to detect a subset of IgG antibodies capable of fixing complement and may be more specific.

Rationale for therapeutic apheresis

Highly sensitized patients in need of cardiac transplantation face challenges in obtaining a compatible allograft. Apheresis techniques have helped to avoid the intensive use of immunosuppressives and provide adjunctive therapy in desensitization and rejection protocols. Although the mechanism of ECP is not precisely understood, data suggest that ECP decreases levels of effector T cells while at the same time expanding Tregs. Tregs are CD4+CD25+Foxp3 lymphocytes that suppress the immune system in an antigen-specific fashion as well as plasmacytoid dendritic cells. The number of circulating Tregs in transplant patients treated with ECP has been shown to increase following ECP. ECP does not appear to increase infection risk. 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. An ECP series is two procedures on consecutive days.

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 MNC dose of need to be treated to mediate the benefits of ECP, it is advisable to ensure that there are circulating MNCs as lymphopenia is not uncommon in this patient population.

Volume treated: ECP: Typically, MNCs are obtained from processing 1.5 L of whole blood, but the volume processed may vary based on patient weight and HCT. The 2-process method collects and treats MNCs obtained from processing 2 TBV.

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

Frequency: ECP: 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 occurs. For TPE, improvement in cardiac function, biopsy findings, and donor specific antibody levels are often used to determine timing of discontinuation.

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CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

Incidence: Rare (433 patients in CAPS Registry as of September 2013)		Procedure	Recommendation	Category
		TPE	Grade 2C	II
No. of reported patients[a]: 100–300	**RCT**	**CT**	**CS**	**CR**
	0	0	1(109)[a]	NA

[a]Includes previously reported case reports and CAPS Registry cases (Cervera, 2014).

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 persistent antiphospholipid antibodies such as lupus anticoagulant (LA), anticardiolipin (aCL), and/or anti- β_2-glycoprotein I (anti- β2GPI). Catastrophic APS (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 renal insufficiency, acute respiratory distress syndrome, pulmonary embolism, encephalopathy, stroke, heart failure, myocardial infarction, livedo reticularis, and skin necrosis. 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 although HLA Class II genes and genetic thrombophilia may be predisposing factors. An environmental trigger also seems to be necessary. In the CAPS Registry, 65% of 469 episodes were associated with precipitating factors which preceded the clinical diagnosis of CAPS: infection was the most common finding, identified in 47% of the episodes, followed by neoplasms (18%), surgical procedures (17%), and anticoagulation withdrawal or low international normalized ratio (11%). LA antibodies are present in 82% of episodes, IgG aCL in 82%, IgM aCL in 48%, IgG anti- β2GPI in 11%, and IgM anti- β2GPI in 3%. Other laboratory features of CAPS include thrombocytopenia (present in 65% of cases) and schistocyes on the peripheral blood smear (22%). The differential diagnosis includes DIC, HIT, HELLP syndrome, TTP, HUS, and sepsis.

Current management/treatment
The optimal treatment of CAPS is unknown since there have been no prospective studies due to the low incidence of the condition. However, the therapeutic approach has three clear aims: treat any precipitating factors, prevent and control ongoing thrombosis, and suppress the excessive cytokine production. Anticoagulation with heparin serves to both inhibit clot generation and promote clot fibrinolysis. Glucocorticosteroids at a usual dosage of 1,000 mg methylprednisolone for 3–5 days are administered to control inflammation. A therapeutic strategy that combines anticoagulation plus glucocorticosteroids with TPE, IVIG, or both, has been associated with improved mortality. Current recommendations are to start TPE when there is no response to anticoagulation plus glucocorticosteroids. Use of TPE may be first-line therapy in patients with severe presentations and in patients with features of microangiopathic hemolytic anemia (Cervera, 2012). When IVIG is used in conjunction with TPE it should be administered after the last treatment to avoid removal. Use of cyclophosphamide may be considered, particularly in patients with concurrent SLE or for patients with high titers of antiphospholipid antibodies to avoid rebound after TPE or IVIG. The role of rituximab and eculizimab, particularly for relapse prevention, remains unclear and research is ongoing.

Rationale for therapeutic apheresis
The exact mechanism for TPE benefit in CAPS is not known, although the removal of antiphospholipid antibodies, cytokines, tumor necrosis factor-α, and complement likely plays an important role.

Technical notes
Plasma as the replacement fluid repletes natural anticoagulants such as antithrombin and proteins C and S. Two successful reports using albumin as replacement fluid claim that plasma may not be always necessary in CAPS (Marson, 2008). 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 possible 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.

Volume treated: 1–1.5 TPV   **Frequency**: Daily or every other day
Replacement fluid: Plasma alone or in combination with albumin (albumin alone is rarely used)

Duration and discontinuation/number of procedures
Most published cases have reported daily or every other day TPE for one to three weeks but some patients have been treated with longer courses. Clinical response dictates the duration of TPE; no single clinical or laboratory parameter is used to determine when to discontinue treatment. Some have followed antiphospholipid antibody titers to monitor response to treatment (Flamholz, 1999).

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CHRONIC FOCAL ENCEPHALITIS (RASMUSSEN ENCEPHALITIS)

Incidence: Rare ~2 per 10^6 people under the age of 18		Procedure TPE	Recommendation Grade 2C	Category III
# of reported patients: <100	RCT 0	CT 0	CS 2(9)	CR 3(5)

Description of the disease

This syndrome of chronic encephalitis was originally described by Theodore Rasmussen in 1958. The hallmarks of the syndrome are intractable focal seizures resistant to anticonvulsant drugs, 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 year) 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. MRI of the brain has become a mainstay for diagnostic assessment and follow-up.

Current management/treatment

Treatment aims to reduce seizure activity and frequency and improve the functional long-term outcome, as measured by both motor and cognitive performance. 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. In general, immunotherapy slows disease progression but none has halted nor cured the disease. Intravenous methylprednisolone and oral prednisone given for up to 24 months in a tapering schedule may help to diminish the intractable focal seizures and motor deficits during the first year of onset and before hemiplegia develops. IVIG (dosed 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 3 infusions followed by monthly infusions for the first year) and prednisone (2 mg/kg/day tapered over 1–2 years) if further treatment is needed. Intraventricular interferon-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 a repeat course of therapy. More recent reports indicate that Serum GluR3 immunoreactivity, which was found in only few patients with Rasmussen encephalitis, is a feature of epilepsy syndromes and not specific to Rasmussen encephalitis. However, other brain autoantibodies have also 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 IA 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.

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

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.

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CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

Incidence: 1–2/100,000		Procedure	Recommendation	Category
		TPE	Grade 1B	I
No. of reported patients: > 300	RCT	CT	CS	CR
	3(67)	0	32(1021)	31(32)

Description of the disease
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is typically (50% of patients) characterized by symmetric proximal and distal symmetrical muscle weakness, decreased sensation, and diminished or absent reflexes, that progresses and relapses for over two or more months. Conversely, atypical CIDP is distinguished by distal neuropathy or asymmetric/multifocal polyneuropathy. 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 Paraproteinemic polyneuropathies fact sheet). CIDP is distinct from Guillain–Barré syndrome (acute inflammatory demyelinating polyneuropathy; AIDP) in that it is a chronic rather than an acute disorder (see AIDP fact sheet). 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 of neurological symptoms, at which point treatment can be tapered or discontinued. About 60–80% 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 examination. Secondary therapies include rituximab, cyclosporine, interferon, azathioprine, cyclophosphamide, methotrexate, 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 have demonstrated that 40–65% require ongoing or maintenance therapy.

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. An increase in inflammatory cytokines has been observed, including HGF, TNF-α, IL-1β, MIP-1α, and MIP1β. 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. 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 10 of the alternate procedure for 4 weeks: 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 and there was no significant difference between the two treatments.

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.

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COAGULATION FACTOR INHIBITORS

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

No. of reported patients: 100–300	RCT	CT	CS	CR
TPE	0	0	7(83)	38(41)
IA	0	0	9(115)	45(64)

Description of the disease

Coagulation factor inhibitors (antibodies) target specific coagulation factors leading to factor deficiency and potentially hemorrhage. Patients with moderate to severe congenital FVIII or IX deficiency (hemophilia A and B, respectively) may make alloantibodies to the exogenous factor replacement (either recombinant or plasma derived). This serious complications occurs in 20–30% of hemophilia A and 3–5% of hemophilia B patients.

Rarely patients without congenital factor deficiency make inhibitory antibodies that are autoantibodies, xenotropic alloantibodies following foreign factor exposure, or associated with plasma cell dyscrasia or myeloproliferative neoplasm (MPN). Autoantibodies are usually against FVIII, which has a biphasic age distribution (elderly and in post-partum period). Cross reactive xenotrophic alloantibodies against FV and prothrombin (FII) occurred in patients exposed to early formulations of bovine-derived fibrin glue. FV antibodies are associated with therapy with streptomycin, cefotaxime, tacrolimus, and infections (tuberculosis and HIV). Patients with lupus anticoagulants (LA) may have selective FII autoantibodies and present with bleeding and concomitant antiphospholipid syndrome. 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 (laboratory assays of coagulation function may not accurately reflect the hemostatic derangement and bleeding risk). Acquired FX deficiency is associated with systemic light chain amyloidosis due to selective binding of FX to amyloid fibrils (laboratory measurements of coagulation function and factor X activity levels are poor predictors of bleeding risk).

Bleeding tendency with factor inhibitors is due to clearance of the specific factor and/or direct inhibition of the factor function. Inhibitory antibodies are quantified and expressed as Bethesda units (BU); <5 BU is considered low titer.

Current management/treatment

Therapy for patients with coagulation inhibitors is based on diagnosis, presence of bleeding, and inhibitor titer. Current treatment options for bleeding in patients with immune-mediated inhibitors include high doses of FVIII for low titer and FVIII bypassing factors (prothrombin complex concentrates and recombinant factor VIIa) for high titer inhibitors. Treatment for suppression of inhibitor production includes high dose corticosteroids, rituximab, cyclophosphamide, cyclosporine, and/or high dose IVIG. The largest long-term series of treatment for acquired inhibitors by Zeitler (2004) found 83% 1 year remission rate using 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 immunosuppressives, IVIG, and platelet and/or plasma transfusion. Patients with AVWS and hemorrhage are usually managed with desmopressin, antifibrinolytics, factor replacement therapy, FEIBA, IVIG, or recombinant factor VIIa. Hypoprothrombinemia associated with LA is treated with prothrombin complex concentrate and corticosteroids. MPN and plasma cell dyscrasias are treated as above to control bleeding, as well as treating underlying disorder.

Rationale for therapeutic apheresis

The extracorporeal removal of antibodies with IA is better studied than TPE. Two IA techniques, neither of which are FDA approved, 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 Ig 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. CS and CR indicate that IA can 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 are unresponsive 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 dyscrasias or MPNs who are bleeding and refractory to standard interventions, especially those with IgM MGUS because of the efficient removal of IgM. A case of FV deficiency due to cross-reacting xenotropic antibodies treated with TPE was reported but with unclear beneficial. TPE is not benficial 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.

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 is controlled with other therapeutic modalities.

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As of May 27, 2015, 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.

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COMPLEX REGIONAL PAIN SYNDROME

Incidence: 6–26/100,000/year	Indication	Procedure	Recommendation	Category
	Chronic	TPE	Grade 2C	III
No. of reported patients: <100	RCT	CT	CS	CR
	0	0	2(39)	2(3)

Description of the disease
Complex regional pain syndrome (CRPS) is a debilitating disease associated with vasomotor, sudomotor, and sensory disturbances in an affected limb or region of the body. Patients with CRPS typically present with pain and prominent autonomic and inflammatory changes in the affected region such as extreme hyperalgesia and allodynia, skin color and temperature change, sweating, edema and inhibited hair, skin, or nail growth. Patients can also have systemic symptoms involving organ systems, including respiratory, cardiovascular (tachycardia, orthostatic intolerance), gastrointestinal (dysmotility), genitourinary (urinary retention), weakness, fatigue, and others.

CRPS may be preceded by a traumatic event, such as fracture, soft tissue injury, or operation. It occurs in 4–7% of patients who have a limb fracture or limb surgery. Even though the majority of CRPS will resolve within weeks to months (acute CRPS), some may last longer and become chronic CRPS (>1 year in duration). Patients with acute CRPS often have a warm, red, and edematous affected body region while patients with chronic CRPS often have a cold, dusky, sweaty affected body region; punch biopsy may show small fiber neuropathy in some cases. CRPS is more common in women than in men, and association with HLA-DQ8 or HLA-B62 has been reported. CRPS may also occur in children, with lower extremity involvement and systemic dysautonomia reported.

The pathophysiological mechanisms of CRPS are not fully understood, and autoantibodies against β2-adrenergic, α1-adrenergic, and muscarinic M2 receptors have recently been associated with this condition. Currently there is no standard testing or diagnostic modality; CRPS remains a clinical diagnosis with the exclusion of other causes.

Current management/treatment
Chronic or severe CRPS is challenging to manage. Multidisciplinary approach is recommended. Many therapeutic agents have been used with variable and often partial effects including bisphosphonates, gabapentin, calcitonin, intravenous ketamine, free radical scavengers, oral corticosteroids, and spinal cord stimulation.

Due to the suspected auto-immune nature of the disease (in at least a subset of patients), steroids, IVIG, and rituximab have been tried and shown to have variable responses. A randomized controlled trial of low-dose IVIG is currently ongoing in adults with CRPS.

There are a few studies that have reported the efficacy of TPE on this condition. Thirty-seven out of 44 (84%) of CRPS patients who underwent TPE (5–7 TPEs over 2–3 weeks) had reported positive response in terms of pain and improvement of other systemic symptoms. The majority required ongoing maintenance TPEs and/or immunosuppressive medications and adjunctive therapies, to maintain symptomatic improvement.

Rationale for therapeutic apheresis
TPE can remove auto-antibodies to β2-adrenergic, α1-adrenergic, and muscarinic M2 receptors (and possibly cytokines), and thus relieve localized and systemic symptoms. As expected, the effect may be transient. Maintenance TPEs may be required, in combination with other therapies.

Technical notes

Volume treated: 1–1.5 TPV	Frequency: 5–7 TPEs over a 2–3 week period, and then as indicated for maintenance management
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures
Five to seven TPEs over a 2–3 week period, and then as indicated for maintenance management (as frequent as weekly).

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CRYOGLOBULINEMIA

Incidence: About 50% of patients with chronic HCV	Procedure	Indication	Recommendation	Category
	TPE	Severe/symptomatic	Grade 2A	II
	IA	Severe/symptomatic	Grade 2B	II
No. of reported patients:>300	RCT	CT	CS	CR
TPE	1(57)	0	24(302)	NA
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. End-organ complications 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 vasculitis. When cryoglobulinemic vasculitis is present, the disease is referred to as CryoVas. Cryoglobulins are classified into three types: Type I consists of monoclonal immunoglobulins, usually due to multiple myeloma (IgG) or Waldenström's macroglobulinemia (IgM), Type II contains polyclonal IgG and monoclonal IgM rheumatoid factor usually due to HCV infection, and Type III contains polyclonal IgG and IgM usually due to inflammatory disorders, autoimmune disease, or HCV infection. About 80–90% of individuals with mixed cryoglobulinemia (Types II and III) have HCV. The diagnosis of cryoglobulinemia is made by history, physical findings, low complement levels, and detection and characterization of cryoglobulins (including quantitation by the cryocrit). There is no correlation between the severity of disease and cryocrit. Individuals with Type I have a higher cryocrit than individuals with Types II or III.

Current management/treatment
Management is based on the severity of symptoms and treating the underlying disorder. Screening for infectious agents is critical in the setting of mixed CryoVas. 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. In a multicenter RCT, rituximab (1 g IV at baseline and Day 14) was compared with conventional treatment (corticosteroids plus azathioprine, cyclophosphamide, or TPE) in 59 patients with severe mixed CryoVas. Survival at 12 months was statistically higher in the rituximab group compared with conventional therapy (64.3% vs. 3.5%, respectively). 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 CryoVas. A separate RCT in patients with severe HCV-associated CryoVas demonstrated statistically significant remission rates in patients in the rituximab group compared with conventional therapy (83% vs. 8%, respectfully). HCV RNA levels were not affected by rituximab therapy. However more recent use of triple HCV therapy with PegIFN/ribavirin and a specifically targeted antiviral agent (NS3/4A protease inhibitor, i.e., boceprevir or telaprevir) has led to improved sustained virological response rates (65–70%) and are used for the treatment of cryoglobulinemia related to HCV genotype 1 infection. When cryoglobulinemia is associated with severe clinical manifestations such as skin ulcerations, glomerulonephritis, or neuropathy, TPE has been used as an adjunct to control the symptoms by directly removing the cryoglobulins.

Rationale for therapeutic apheresis
TPE removes cryoglobulins efficiently with case reports and case series suggesting improvement in 70–80% of treated patients. It has been used mostly in active moderate to severe cryoglobulinemia with renal impairment (membranoproliferative glomerulonephritis), neuropathy, arthralgia, and/or ulcerating purpura. TPE can be performed either alone or in conjunction with immunosuppressive therapy and has been used in both short- and long-term management.

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 two 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. In a randomized, parallel group study IA apheresis confirmed to be effective for lowering cryoglobulins (Stefanutti, 2009).

Technical notes
It is prudent to warm the room, draw/return lines, and/or replacement fluid to prevent intravascular precipitation of the cryoglobulins. Precipitation of cryoglobulins in the extracorporeal circuit has been reported.

Volume treated: 1–1.5 TPV
Replacement fluid: Albumin

Frequency: Every 1–3 Daily

Duration and discontinuation/number of procedures
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 treatment 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.

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CUTANEOUS T CELL LYMPHOMA; MYCOSIS FUNGOIDES; SEZARY SYNDROME

Incidence: MF: 6/1,000,000/yr; SS: 0.8/1,000,000/yr	Indication	Procedure	Recommendation	Category
	Erythrodermic	ECP	Grade 1B	I
	Non-erythrodermic	ECP	Grade 2C	III

# of reported patients: > 300	RCT	CT	CS	CR
Stage III (erythrodermic) MF + SS	1(8)	4(64)	32(698)	1(2)
Non-erythrodermic 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 $\geq$ 10%); II has either lymphadenopathy with low-grade pathological CD4+ T cell infiltration (IIA) or skin tumors (IIB); III has generalized erythroderma ($\geq$ 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 stage I MF when >5% of peripheral blood lymphocytes are Sézary cells. Because advanced MF, SS, and their treatments are associated with significant immune compromise, death can occur from infectious complications (often arising 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. Limited-stage disease (IA to IIA) is treated with 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 >5% of peripheral blood Sézary cells 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), 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. Primary intervention for SS 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 mechanism of action in MF and SS is unclear, though it appears to be mediated by in vivo stimulation of anti-tumor immunity. Recent reports have shown that ECP induces monocyte to dendritic cell maturation. In addition, ECP may decrease CD4+FOXP3+CD25− cells and increase functional CD8+ T cells. The overall response rate of ECP in CTCL ranges from 36 to 73%, with complete response rates of 14–26%. 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). ECP can be combined with biological response modifiers such as retinoids and interferons to achieve more complete responses. 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: Typically, MNCs are obtained from processing 1.5 L of whole blood, but the volume processed may vary based on patient weight and HCT. The 2-process method collects and treats MNCs obtained from processing 2 TBV.

Replacement fluid: NA

Frequency: Two consecutive days (one cycle) every two to four 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.

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DERMATOMYOSITS/POLYMOYSITIS

Incidence: 1/100,000/yr in adults, 0.4/100,000/yr in children		Procedure	Recommendation	Category
		TPE	Grade 2B	IV
		ECP	Grade 2C	IV
No. of reported patients: < 100	**RCT**	**CT**	**CS**	**CR**
TPE	1(39)	0	1(3)	2(2)

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 (mainly CK and aldolase) is present. Compared to PM, DM is associated with skin manifestations.DM in adults could be associated with 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. Corticosteroids and other immunosuppressive and immunomodulatory treatments are commonly used to improve manifestations of the disease and allow reduction in corticosteroid dosing. Most patients respond to corticosteroid therapy initially. Recurrent or resistant disease may require higher corticosteroid doses, azathioprine, methotrexate, rituximab, or intravenous immune globulin. Remission occurs in most of the patients after months of immunosuppressive and intensive supportive therapy, especially in juvenile DM.

Rationale for therapeutic apheresis
Autoantibodies such as ANA, anti-Ro, anti-La, anti-Sm, anti-ribonucleoprotein, or myositis-specific antibodies are commonly present, but not specific to the disease. 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. Macrophages are involved in vascular infiltrations. In one randomized controlled trial (Miller, 1992), TPE was no more effective in improving muscle strength or functional capacity (although serum levels of muscle enzymes improved) than sham apheresis. Recently three cases were published with therapy refractory (2) and relapsed (1) DM. Immunsuppressive therapy including IVIg alone demonstrated no clinical improvement in these patients. Following the addition of TPE (twice weekly for 1 month and then tapering to once weekly up to months), the authors claimed TPE as a rescue therapy. Muscle enzymes decreased and muscle strength increased in months, resulting in complete remissions in all three cases. Despite this favorable outcome, it is not clearly shown that TPE was responsible for the remission. Two cases were reported where the main pathology was macrophage activation syndrome. These two patients went into clinical remission, but it is not clear, what was influenced, the MAS or the underlying disease.

One isolated case was reported of a patient with juvenile DM, who received photopheresis in addition to methotrexate treatment. After 20 months of treatment with ECP, the patient's cutaneous lesions remained unchanged. The patient did experience return of strength to near normal levels and normalization of liver function tests and aldolase levels. In a recent published review (Spratt, 2015), photopheresis was not recommended as treatment for DM.

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DILATED CARDIOMYOPATHY, IDIOPATHIC

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

No. of reported patients: > 300	RCT	CT	CS	CR
IA	3(65)	10(400)	17(403)	NA
TPE	0	0	1(8)	2(2)

Description of the disease
Dilated cardiomyopathy (DCM) is characterized by progressive ventricular enlargement with impaired ventricular contractile function. Clinically patients present with signs and symptoms of congestive heart failure (dyspnea, orthopnea, impaired exercise tolerance, fatigue, and peripheral edema) and arrhythmias. Fifty percent of cases are idiopathic (iDCM). One-third of iDCM cases result from inherited mutations in cytoskeleton proteins. The pathogenesis of the remaining iDCM cases appears to involve autoimmunity triggered by viral myocarditis. Viral genome can be detected on endomyocardial biopsy in up to 67% of patients with iDCM and 80% have autoantibodies toward various myocardial antigens (α-Myosin, β1-adrenergic receptor, Troponin-I, Na-K-ATPase, M2-muscarinic acetylcholine receptor).

Current management/treatment
iDCM is usually managed medically 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. Treatment of iDCM with immunosuppression and/or IVIG has had mixed results.

Rationale for therapeutic apheresis
Most research to date on the application of apheresis in iDCM has examined the use of IA to remove cardiac autoantibodies. Trials and case series using IA columns have demonstrated short- and long-term clinical 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. Factors associated with response to IA therapy have included shorter duration of disease, the presence of low immunoglobulin affinity Fcγ-receptor IIa polymorphisms, and greater impairment of left ventricular function.

One controlled trial using anti-human polyclonal immunoglobulin (AHPI) IA in 34 patients found persistent reduction in β1-adrenergic receptor antibodies and improved left ventricular ejection fraction (LVEF) at 12 months with statistically significant differences in survival at 5 years between the treated group (82%) and matched controls (41%, $P < 0.0001$) (Muller, 2000). In addition to medical benefit, economic analysis found that the IA treatment was cost effective (Hessel, 2004). Another controlled trial examined outcomes in 108 patients with β1-adrenergic receptor antibodies undergoing IA 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% for those with antibodies who underwent IA treatment compared to 25% for those with antibodies who did not ($P < 0.05$). Patients who underwent IA but who lacked β1-adrenergic receptor antibodies had a 47% probability of being cardiac transplant or LVAD free at 5 years ($P < 0.05$). Clinical improvement and reduction in antibody levels are observed whether using columns specific for β1-adrenergic receptor antibody removal or nonspecific IA (Dandel, 2012).

A case series of eight patients treated with TPE 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 (Torre-Amione, 2010).

Technical notes
Studies have examined only optimally medically managed patients with symptoms for ≥ 6 months. Patients with iDCM due to inherited cytoskeletal abnormalities have not been treated with IA and would not be expected to respond. IVIG (0.5 g/kg) was given after last treatment in the majority of IA studies and the TPE case series.

Four different IA columns (AHPI, Staphylococcal protein A agarose (SPAA), β1-adrenergic receptor antibody, and tryptophan polyvinyl alcohol) have been used. Comparison studies of IA columns found SPAA less effective due to a lower affinity for pathogenic IgG3 antibodies. Modified SPAA protocols with enhanced IgG3 removal were more effective. TPE has been used when IA was unavailable or when the extracorporeal volume of the IA device was too large for the patient being treated.

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 five consecutive days to four courses of five consecutive days repeated every four weeks failed to demonstrate differences in LVEF at 3 and 6 months between the two treatment schemas. Repeat IA and TPE have been reported to be effective in patients experiencing increasing β1-adrenergic receptor antibody titers and/or worsening LVEF.

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ERYTHROPOIETIC PORPHYRIA, LIVER DISEASE

Incidence: 2–5/1,000,000		Procedure	Recommendation	Category
		TPE	Grade 2C	III
		RBC Exchange	Grade 2C	III

# of reported patients: < 100	RCT	CT	CS	CR
TPE	0	0	1(3)	14(15)
RBC Exchange	0	0	1(3)	7(9)

Description of the disease

Erythropoietic protoporphyria (EPP) is a rare autosomal recessive disorder characterized by partial deficiency of ferrochelatase, a mitochondrial enzyme in the heme biosynthetic pathway. The majority of affected individuals are compound heterozygous for a common low expression *FECH* allele and a second loss of function *FECH* allele. This terminal enzyme catalyzes insertion of iron into protoporphyrin ring to generate heme. Defective activity of ferrochelatase mainly in erythropoietic cells leads to the accumulation of protoporphyrin in RBCs and secondarily in plasma, skin, hepatocytes, bile, and stool. An analogous pathophysiology results from gain of function mutations in the x-linked gene, *ALAS2,* which encodes the first enzyme of the heme synthetic pathway; this disease is termed x-linked protoporphyria (XLP). Clinical manifestations in EPP and XLP are the same and include a nonblistering painful photosensitivity, commonly presenting in childhood. Skin symptoms are caused by the photoactivation of the protoporphyrin molecule by visible light, mainly in the blue-violet region (∼400 nm) generating reactive oxygen species that can interact with biological molecules, including proteins, lipids, and DNA. Protoporphyrin is lipophilic and is poorly water-soluble and has no urinary excretion; the major means of excretion is by hepatic clearance and bile excretion. Mild hepatobiliary disease is noted in 20–30% of patients. Liver damage has been attributed to precipitation of insoluble protoporphyrin in bile canaliculi and to protoporphyrin-induced oxidative stress. Severe cholestatic liver failure develops in <5% of patients and patients with XLP or EPP with biallelic loss of function *FECH* alleles may face a higher risk of this complication. Except for the small percentage of patients with advanced liver disease, life expectancy is not reduced.

Current management/treatment

Treatment of the photosensitivity in EPP and XLP patients consists mainly of preventing skin damage by avoiding light exposure, wearing protective clothing and barrier sunscreens. β-carotene helps some people but causes yellow discoloration of the skin. Hypertransfusion therapy has also been used to treat severe photosensitivity but cannot be considered a long-term treatment. More recently, afamelanotide, a melanocyte-stimulating hormone analogue has been shown to increase the quality of life and duration of pain-free time in light and is EMA-approved in Europe but is currently not FDA-approved in the US. Mild to moderate liver disease is treated with oral ursodiol to alter bile composition and cholestyramine to alter enterohepatic circulation of protoporphyrin. Additionally, oral antioxidants can be used (vitamin C and *n*-acetyl cysteine).

Cholestatic liver failure is uncommon in EPP and XLP and the optimal therapeutic approach remains unknown. Current treatments are directed at decreasing the plasma protoporphyrin level or reducing oxidant damage. Agents used to treat mild to moderate liver disease are employed. Additionally, hypertransfusion may provide a benefit by suppressing endogenous erythropoiesis and in turn protoporphyrin production. Hematin infusions may be helpful in suppressing heme synthesis in nonerythroid cells by a negative feedback mechanism on ALAS1. All of these therapies are non-curative. For those patients with liver failure, liver transplantation can re-establish liver function but it does not correct the enzymatic deficiency in erythroid cells and disease recurrence in the graft occurs for the majority of recipients. Hematopoietic stem cell transplantation is curative for these disorders and can correct the liver failure in a subset of patients. Case reports have described successful outcomes after hematopoietic stem cell transplantation alone or in combination with liver transplantation.

Rationale for therapeutic apheresis

The goal of TPE or RBC exchange during acute liver failure is to decrease the protoporphyrin level in the plasma and to prevent further deposition in the liver; TPE may also be advantageous in removal of bile acids with improvement in pruritus. Multiple sessions of TPE, in combination with intravenous hematin may be used. Plasma protoporphyrin level decrease is followed by reduction of protoporphyrin levels in RBCs. Some speculate that RBCs may serve as a sink to absorb excess plasma protoporphyrins, providing a rationale to consider RBC exchanges to reduce plasma protoporphyrin levels. Neither TPE nor RBC exchange alone or in combination are likely to benefit patients with advanced-stage disease; however case reports support the potential benefits of using TPE and/or RBC exchange to bridge patients prior to OLT or HSCT. Whether these therapies may be of clinical benefit if initiated earlier in disease and before extensive tissue damage due to deposition of protoporphyrins occurs is uncertain but it warrants further investigation.

Technical notes

For RBC exchange, automated apheresis instruments calculate the amount of RBCs required to achieve the desired postprocedure Hct and fraction of the original red cells remaining. Target the fraction of the remaining cells to 25–30% with a final Hct of 35%. Avoid exposure of patient to excess light during procedure.

Volume treated: TPE: 1–1.5 TPV; RBC Exchange: 1–1.5 RBC volume   **Frequency**: TPE: Every 1–3 days; RBC Exchange: 3×/week
Replacement fluid: TPE: Albumin, plasma

Duration and discontinuation/number of procedures

Variable.

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FAMILIAL HYPERCHOLESTEROLEMIA

Incidence: Heterozygotes: 200/100,000/year; Homozygotes: 1/1,000,000/year	Indication	Procedure	Recommendation	Category
	Homozygotes[a]	LDL apheresis	Grade 1A	I
	Heterozygotes	LDL apheresis	Grade 1A	II
	Homozygotes with small blood volume[b]	TPE	Grade 1C	II

No. of reported patients: > 300	RCT	CT	CS	CR
LDL apheresis	6(228)	15(308)	22(401)	NA
TPE	0	1(5)	14(62)	NA

[a]Approved indications vary among countries, see technical notes below. [b]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 year, and death from coronary heart disease by age 20. Heterozygotes (HT) exhibit cholesterol of 250–550 mg/dL, xanthomata by age 20, and atherosclerosis by age 30. More recently, gain-of-function mutations in proprotein convertase subtilisin-like/kexin type 9 (*PCSK9*) have been identified that result in familial autosomal dominant hypercholesterolemia (ADH), a disease characterized by elevated LDL-C concentration.

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 10% and 25–49%, respectively. Recently approved, PCSK9 inhibitors are monoclonal antibodies that dramatically lower LDL cholesterol. 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, ICAM-1). Because of the slow rise in LDL following treatment (1–2 weeks), 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.

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} = time-averaged cholesterol, C_{min} = cholesterol level immediately after apheresis, K = rebound coefficient, and C_{max} = cholesterol level immediately prior to treatment. Values for K for HM and HT have been determined to be 0.65 and 0.71, respectively. To achieve these, reductions of total cholesterol of $\geq$65% or LDL of $\geq$70% must be achieved with each procedure. Some examples of patient criteria. FDA criteria are: (1) functional HM with LDL >500 mg/dL (>13 mmol/L), (2) functional HT with no known cardiovascular disease but LDL $\geq$300 mg/dL (>7.8 mmol/L), and (3) functional HT with known cardiovascular disease and LDL $\geq$160 mg/dL (>5.2 mmol/L). International Panel on Management of FH (Spain) are: (1) 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. German Federal Committee of Physicians and Health Insurance Funds criteria are: (1) HM and (2) patients with severe hypercholesterolemia in whom maximal dietary and drug therapy for >1 year has failed to lower cholesterol sufficiently. HEART-UK criteria are: (1) HM in whom LDL is reduced by <50% and/or >9 mmol/L (348 mg/dL) with drug therapy, (2) HT or "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. During pregnancy, LDL levels in individuals affected by FH can rise to extreme levels (1,000 mg/dL) that can compromise uteroplacental perfusion. LDL apheresis may 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 occuring in homozygous FH.

Technical notes

Multiple removal systems are available that have equivalent cholesterol reduction and side effects. Please refer to the Appendix in the Introduction section for information on the different LDL cholesterol selective removal systems in use. 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, requiring supplementation of vitamin B12 and iron.

Volume treated: LDL apheresis: Varies according to device; TPE: 1–1.5 TPV	**Frequency**: Adjusted to reduce the time averaged LDL cholesterol by $\geq$60%, usually once every 1–2 weeks.
Replacement fluid: LDL apheresis: NA; TPE: Albumin	

Duration and discontinuation/number of procedures

Treatment is continued indefinitely.

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FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Incidence: 7/1,000,000	Indication	Procedure	Recommendation	Category
	Recurrent in transplanted kidney	TPE	Grade 1B	I
	Steroid resistant in native kidney	LDL Apheresis	Grade 2C	III

No. of reported patients: >300	RCT	CT	CS	CR
Recurrent in transplanted kidney	0	3(48)	49(224)	15(17)
Steroid resistant in native kidney	0	0	1(11)	4(4)

Description of the disease

Focal segmental glomerulosclerosis (FSGS) is a histologically characteristic finding in renal biopsy specimen 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) exist, which have different clinical presentations and treatment response. 80% of FSGS cases are idiopathic. Other causes include mutations in specific podocyte genes, secondary to drugs, and hemodynamic adaptive response. Idiopathic FSGS is postulated to result from a plasma factor or factors of unknown origin that injure(s) the filtration barrier and/or increases glomerular permeability. This hypothesis is supported by the observation that FSGS may recur in a renal allograft. Inconsistent data favor a permeability factor, thought to be suPAR, a membrane bound receptor for uPA (urokinase), circulates as multiple fragments of different sizes. ESRD occurs within 3–7 years. Recurrence occurs in up to 40% of renal allografts. Idiopathic FSGS poses the highest risk of recurrence post-transplant. Other risk factors for recurrence are younger age, short duration of native kidney disease, history of recurrence with previous transplant, heavy proteinuria, bilateral native nephrectomy, race, and living donor kidney. FSGS recurrence can happen a few hours to 2 years post-transplant. Recurrent FSGS in the transplanted kidney is diagnosed histologically or when nephrotic range proteinuria develops. If untreated, recurrent FSGS will ultimately lead to permanent graft loss within months. Those who lost grafts to recurrence have >80% chance of recurrent FSGS in subsequently transplanted kidneys.

Current management/treatment

Patients with primary FSGS with proteinuria >3 g/day do not benefit from TPE and are treated with corticosteroids. For secondary FSGS, underlying cause should be treated. The main goal of recurrent FSGS treatment is to achieve complete or partial remission of proteinuria and prevent premature allograft loss. Even though the use of TPE in treating FSGS in native kidneys has been disappointing, treatment for recurrent FSGS often responds to a combination of TPE, high dose corticosteroids, other immunosuppressives, and/or angiotensin II receptor antagonist (ARB) or ACE inhibitor. More recently, rituximab, IVIG, and mycophenolate mofetil have also been used in conjunction with TPE.

Rationale for therapeutic apheresis

Patients with reccurent FSGS appear to have a permeability factor, which is removed by TPE and decreasing plasma concentration coincides with proteinuria improvement. Pretransplant TPE may prevent or delay recurrence in high-risk patients but this finding has not been universal. Usually TPE is started once recurrence is diagnosed. The number of TPEs needed to control proteinuria, surrogate marker of FSGS, is variable. Garcia (2006) treated 9 children with 10 TPEs plus high doses of cyclosporine, mycophenolate mofetil, and prednisone, starting <48 h after the diagnosis of proteinuria, and reported a 55% complete remission and 12% partial response rates, compared with no remissions among five children who did not receive TPE. Studies support the need for immunosuppression as well as TPE. Sener (2009) reported on four adults treated with 9–15 TPEs of and mycophenolate mophetil who had preserved renal function as late as 34 months post-transplant. A retrospective study of adults with FSGS (Moroni, 2010) suggested that TPE and ACE inhibitors resulted in either complete or partial remission of proteinuria in 80% of patients. Tsagalis (2011) reported 50% complete remission and 50% partial remission in four patients with recurrent FSGS treated with a combination of TPE and rituximab. 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. Another reported approach of intense/maintenance TPE treatment includes the following schedule: 3/week for the first 3 week, followed by 2/week for 3 week, 1/week until month 3, 2/month until month 5, and 1/month until month 9, 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 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. It is recommended that TPE be instituted as soon as recurrent FSGS is diagnosed, in order to halt the process and maintain kidney function.

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GRAFT-VERSUS-HOST DISEASE

Incidence: After allogeneic HSCT: 10–60%	Indication	Procedure	Recommendation	Category
Grade II–IV acute GVHD: 6–80%	Skin (chronic)	ECP	Grade 1B	II
moderate–severe chronic GVHD	Non-skin (chronic)	ECP	Grade 1B	II
	Skin (acute)	ECP	Grade 1C	II
	Non-skin (acute)	ECP	Grade 1C	II
No. of reported patients: > 300	RCT	CT	CS	CR
Chronic second line treatment	1(95)	3(101)	19(629)	NA
Acute second line treatment	0	2(116)	13(189)	NA

Description of the disease

Graft-versus-host disease (GVHD) following hematopoietic stem cell transplant (HSCT) is classified as acute (aGVHD), chronic (cGVHD) or overlap syndrome. Classic aGVHD occurs at ≤ 100 days post-HSCT and manifests as inflammatory tissue injury and necrosis with skin and gastrointestinal (GI) tract inflammation and denudation, cholangiohepatic liver injury, and cholestatic jaundice. Late-onset aGVHD, which occurs, recurs or persists at > 100 days, has typical aGVHD manifestations without diagnostic clinical or histologic features of cGVHD. Classic cGVHD affects skin, GI, liver, lungs, oropharynx, eyes, genital tract, and/or musculoskeletal systems without aGVHD features. Overlap syndrome is the presence of aGVHD with distinctive or diagnostic features of cGVHD. aGVHD results from activation of donor T-cells by host antigen-presenting cells (APCs), leading to T cell- and cytokine-mediated tissue injury. cGVHD 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 are developed to systematically grade GVHD subtypes. Severe GVHD has a high risk of death or severe morbidity due to end-organ complications and/or infections.

Current management/treatment

aGVHD of Grades II–IV is treated with corticosteroids and calcineurin inhibitors. 50% of patients will not completely respond and may progress to cGVHD. Other immunosuppresives and ECP are salvage therapies. Moderate to severe cGVHD is managed with corticosteroids with or without other systemic immunosuppressives. Treatments for steroid-refractory or -dependent extensive cGVHD include other immusuppressives and ECP.

Rationale for therapeutic apheresis

ECP works through ex vivo treated lymphocytes, which undergo apoptosis and modulate in vivo immune responses (increased dendritic cell differentiation, down regulation of autoreactive B cells, alterations in T helper subset populations and lymphocyte homing antigen display, switch from pro-inflammatory to anti-inflammatory cytokine production, and generation of regulatory T cells). Overall response rates for steroid-refractory aGVHD reportedly range from 52 to 100%; with responses in 66–100% skin, 40–83% GI tract, and 27–71% liver. Complete responses and improved survival are often reported among aGVHD cohorts; however, the results for ECP are not superior to results reported for alternative salvage approaches for steroid-refractory aGVHD. About 30–65% of steroid-dependent cGVHD patients improve with ECP, most with partial responses. One study observed superior outcomes for patients with overlap or classic cGVHD compared to aGVHD subtypes. Two different second-line or salvage therapies were compared: group receiving ECP ($n = 57$) had a significantly better survival rate (HR 4.6, $P = 0.016$) and skin and gut involvement than group receiving cytokine therapy (inolimumab or etanercept) ($n = 41$) (Jagasia, 2013).

ECP for cGVHD have response rates of 48–100% in skin, 0–90% in liver, 21–90% in oral mucosa. Importantly, corticoid sparing effect occurs, even in absence of organ improvement, and therefore increased quality of life. Maximal responses for cGVHD require 2–6 months of treatment. RCT using ECP for steroid-resistant skin cGVHD observed no statistically significant difference in total skin score at 12 weeks of ECP plus salvage therapy compared to salvage therapy alone. However, unblinded assessments recorded 40% complete and partial response in the ECP compared to 10% in the non-ECP group. More rapid skin improvement was also observed and corticosteroids could be more quickly tapered. Among 29 control patients who crossed over to receive 24 weeks of ECP for refractory disease, objective responses occurred in the skin and extracutaneous tissue in 33% and 70%, respectively. Many clinical practice guidelines and consensus statements addressing the use of ECP for GVHD have been published. Collectively, these consider ECP as an established second-line therapy option for steroid-refractory cGVHD, particularly involving the skin. Some recommend consideration of ECP as adjunctive first-line modality for GVHD associated bronchiolitis obliterans syndrome. In cGVHD in a limited patient number a response rate of 51% was reported (CR 14, PR 20, improvement 17).

Technical notes

Inline methods (all steps are performed in one system), offline systems (leukopheresis system for MNC collection and a separate illumination system), and MINI ECP (manual MNC preparation from whole blood with a separate illumination system) are used for ECP. Heparin is the standard anticoagulant for inline systems, and ACD-for offline systems, in patients with low platelet count and/or gut bleeding, heparin should be avoided.

Volume treated: Typically, MNCs are obtained from processing 1.5 L of whole blood, but volume processed varies based on patient weight and HCT. 2-process method collects and treats MNCs obtained from processing 2 TBV.	**Frequency**: aGVHD: 2–3 treatments weekly, tapering to 2 weekly, and 2 every 2 weeks; cGVHD: Two consecutive days (one cycle) every 1–2 weeks.
Replacement fluid: NA	

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.

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HASHIMOTO'S ENCEPHALOPATHY; STEROID-RESPONSIVE ENCEPHALOPATHY ASSOCIATED WITH AUTOIMMUNE THYROIDITIS

Incidence: Rare		Procedure TPE	Recommendation Grade 2C	Category II
# of reported patients: < 100	**RCT** 0	**CT** 0	**CS** 0	**CR** 14(15)

Description of the disease

Hashimoto's encephalopathy (HE) is a rare neuropsychiatric syndrome best defined by encephalopathy of unknown etiology associated with the high titers of antithyroid antibodies in the absence of alternative diagnoses such as nervous system infection, tumor, or stroke. The clinical presentation is highly variable but there are typically two distinct presentations. The first is an acute onset of episodes of stroke-like symptoms, seizure, and psychosis. Alternatively, it may present as an indolent form associated with depression, cognitive decline, myoclonus, tremors, and fluctuations in level of consciousness. The mean age of onset is about 40–50 years and like most autoimmune disorders, females are affected more than men (4:1). Imaging, EEG, and CSF studies are usually non-specific but can help to rule out other causes of encephalopathy. Despite the elevated levels of antithyroid antibodies, most patients are euthyroid at the time of diagnosis. The most common antithyroid antibody detected is antithyroid peroxidase, followed by antithyroglobulin antibodies. The role of the antithyroid antibodies as the primary cause of Hashimoto's encephalopathy is controversial. Furthermore, the titer of antithyroid antibodies does not correlate with clinical symptoms of the disease or with its severity. However, persistent elevated titers of the antithyroid antibodies appear to be predictive of relapse, a prolonged disease course, less response to steroids, and a worse prognosis.

Current management/treatment

High dose corticosteroids are the first-line therapy. One of the systematic reviews documented response to steroids in most patients, with 87.6% of cases achieving complete response. Corticosteroid treatment is so fundamental that some have renamed HE as "steroid-responsive encephalopathy associated with autoimmune thyroiditis" (SREAT). Common steroid regiments include IV methylprednisolone (500–1,000 mg/day) and oral prednisone (1–2 mg/kg/day), each either alone or combined (IV followed by oral therapy), which is tapered within weeks or months, according to clinical response. For patients who fail initial therapy with steroids or relapse, secondary therapies had been used with variable efficacy. IVIG for steroid unresponsive patients had shown successful clinical response in some case reports. Azathioprine or cyclophosphamide after steroid pulse therapy has also been successful. Rituximab was utilized to reduce the breakthrough events in patients with HE. In most cases, reduction in antibody titer following immunosuppressive therapy correlated with clinical improvement.

Rationale for therapeutic apheresis

Although the pathogenesis is unknown, an autoimmune process is believed to play a role. The clinical response to immunomodulatory agents such as steroids and IVIG provides indirect evidence to the pathogenic role of the antibodies and make the use of plasma exchange plausible. In the published cases to date, TPE has been tried, in both adult and pediatric cases, in patients who have failed to respond to steroids. Few of the reported cases demonstrate removal of the anytithyroid antibodies but most demonstrate symptomatic improvement.

Technical notes

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

Duration and discontinuation/number of procedures

The published case reports used 3–9 procedures, mostly commonly 5.

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HELLP SYNDROME

Incidence: 0.2–0.8% of all pregnancies, 11–35% of pregnancies with pre-eclampsia	Indication	Procedure	Recommendation	Category
	Postpartum	TPE	Grade 2C	III
	Antepartum	TPE	Grade 2C	IV
No. of reported patients: 100–300	RCT	CT	CS	CR
	0	1(29)	6(79)	9(10)

Description of the disease

The HELLP syndrome (Hemolysis, Elevated Liver Enzymes and Low Platelets) is a peripartum thrombotic microangiopathic syndrome characterized by hemolysis, low platelets, and liver dysfunction. HELLP typically presents in the 3rd trimester of pregnancy but up to $1/4$ of patients may present post-partum. In 70–80% of cases, HELLP coexists with pre-eclampsia but can also occur in the absence of hypertension or proteinuria. Patients with severe HELLP may develop DIC, and multi-organ failure. Other clinical entities that can present with similar features include immune thrombocytopenia, thrombotic thrombocytopenia purpura (TTP), hemolytic uremic syndrome, antiphospholipid syndrome, lupus, acute fatty liver of pregnancy, and HELLP-like conditions caused by severe hypovolemic shock, sepsis, and sickle cell crisis. In contrast to TTP, ADAMSTS-13 levels in HELLP are typically low but detectable (20–50%). The pathogenesis remains incompletely understood but is currently thought to result from endothelial dysfunction and an inflammatory response that leads to thrombotic microangiopathy. Diagnosis is based on the presence of thrombotic microangiopathy (as evidenced by elevated lactate dehydrogenase [LDH], indirect hyperbilirubinemia, and schistocytes on peripheral smear), low platelets and elevated liver enzymes. Women who develop HELLP have a high risk of recurrence in subsequent pregnancies (14–24%).

Current management/treatment

Prompt delivery by cesarean section is the definitive treatment for HELLP. Prolongation of pregnancy has been associated with increased maternal and perinatal mortality. Steroids are used to support fetal lung maturity in pre-term cases. Some centers routinely use high dose steroids but this practice remains controversial due to a recent Cochrane meta-analysis that showed no benefit for maternal morbidity or perinatal death.

Rationale for therapeutic apheresis

TPE is speculated to remove circulating protein bound platelet aggregating and procoagulant factors released from both activated platelets and endothelial cells. Multiple case reports, case series, and one retrospective controlled trial have shown clinical benefit of TPE in severe post-partum HELLP along with clinically significant improvement in platelet counts and decreases in serum LDH and aspartate aminotransferase levels. TPE is utilized when there is a failure of the patient to improve within 48–72 h following delivery. Although TPE seems to confer benefit when applied to severe post-partum cases, many studies were done without ADAMTS-13 measurements to rule out TTP and may have included patients who had TTP. TPE is the primary therapy for TTP and should be initiated when there is clinical suspicion of TTP (see TTP fact sheet). One small study which used ADAMSTS-13 levels to differentiate HELLP from TTP showed recovery in four severe HELLP cases treated with high dose steroids without the use of TPE (Pourrart, 2013). There is no role for TPE in ante-partum HELLP as treatment may delay delivery, the definitive treatment for HELLP.

Technical notes

Volume treated: 1–1.5 TPV	Frequency: Daily if there is no improvement beginning 48–72 h after delivery
Replacement fluid: Plasma	

Duration and discontinuation/number of procedures

TPE in post-partum HELLP is generally performed until platelet counts are $>100 \times 10^9$/L or LDH has normalized.

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HEMATOPOIETIC STEM CELL TRANSPLANT, ABO INCOMPATIBLE

Incidence: 20–50% of allogeneic donor transplants	Indication	Procedure	Recommendation	Category
	Major ABO incompatible HPC(M)	TPE	Grade 1B	II
	Major ABO incompatible HPC(A)	TPE	Grade 2B	II
	Minor ABO incompatible HPC(A)	RBC Exchange	Grade 2C	III
No. of reported patients:>300	RCT	CT	CS	CR
Major ABO incompatible	0	0	5(491)	NA
Minor ABO incompatible	0	0	3(40)	0

Description of the disease

Major ABO incompatibility refers to the presence of natural antibodies (isoagglutinins) in the recipient against the donor's A and/or B blood group antigens, that may cause acute hemolysis of the RBCs present in infused HPC products. HPC products collected by apheresis [HPC(A)] contain a small amount of RBCs (2–5% hematocrit) with total RBC volume typically measuring <20 mL and therefore, acute hemolysis is uncommon. By comparison, bone marrow HPC products [HPC(M)] contain 25–35% RBCs and acute hemolytic reactions are a major concern when the recipient's isoagglutinin titer (IgG or IgM) is >16. Acute hemolysis following the infusion of cord blood is rare. Cord blood HPC products are usually washed to remove excessive RBCs either prior to cryopreservation or after the freeze/thaw process which will then also remove the products of hemolysis in the thawed product. After major ABO incompatible transplant, RBC engraftment may be delayed in up to 20–30% of cases and some patients develop pure RBC aplasia (PRCA) due to persistence of isoagglutinins that destroy donor erythroid precursors (see PRCA fact sheet). Pretransplant isoagglutinin titers are not always predictive of the development of delayed engraftment or PRCA after major ABO incompatible transplant.

Minor ABO incompatibility refers to the presence of isoagglutinins in the plasma of a HPC product against the recipient's A and/or B antigen. These products may induce acute hemolysis of recipient RBCs if the donor isoagglutinin titer is high (i.e., >128) and infused plasma volume exceeds 200 mL (adult recipient). An additional clinically significant risk with minor ABO incompatibility is the development of a delayed, severe, and potentially fatal alloimmune hemolysis, termed passenger lymphocyte syndrome (PLS). PLS typically occurs at 7–10 days post HPC infusion, and is caused by donor B lymphocytes that mount an antibody response against host A or B antigens.

Current management/treatment

In major incompatibility, acute hemolysis can be avoided by removing RBCs from the HPC product or by reducing the recipient's isoagglutinin titer. 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. Recipient isoagglutinin reduction is performed largely by TPE. IA is also available in some countries. In some European centers, isoagglutinin titer reduction may be accomplished by slowly infusing donor-type RBCs to adsorb antibodies in vivo.

In minor incompatible transplants with donor isoagglutinin titer >128 and HPC plasma volume >200 mL, product plasma reduction is performed to prevent recipient hemolysis. Plasma reduction does not reduce the B lymphocyte content of HPC and does not reduce the incidence of PLS. PLS is unpredictable and managed expectantly with aggressive transfusion support or RBC exchange using group O RBCs pretransplant to reduce the volume of donor incompatible RBCs. PLS has been anecdotally treated with TPE to rapidly reduce isoagglutinin titer.

Rationale for therapeutic apheresis

For major incompatible transplant, TPE to reduce recipient's isoagglutinin titer prior to infusion of the HPA product can be used as an alternative to RBC reduction of the HPC product.

For minor ABO incompatible transplantation, prophylactic RBC exchange can effectively reduce the number of host RBCs that would be the target of the PLS. The published experience suggests that a pretransplant residual host RBC population of 35% or less can significantly mitigate delayed hemolysis in high risk patients. A small study, however, did not demonstrate any clear benefit of RBC exchange in reducing hemolysis when performed 4 days post infusion of the HPC product.

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 to 35% residual host RBCs.

Volume treated: TPE: 1–1.5 TPV; RBC exchange: 1–1.5 RBC volumes	Frequency: TPE: Daily; RBC exchange: Once
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 recommended safety endpoint for TPE is to reduce the recipient's IgM or IgG antibody titers to <16 immediately before HPC product infusion. If there is a delayed red cell recovery or PRCA post-transplant, TPE may be performed.

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HEMATOPOIETIC STEM CELL TRANSPLANT, HLA DESENSITIZATION

Incidence: DSA* in 3–24% of allogeneic HSCTs		Procedure TPE	Recommendation Grade 2C	Category III
No. of reported patients: < 100	RCT 0	CT 0	CS 2(13)	CR 7(11)

*Donor-specific antibody (HLA).

Description of the disease

Hematopoietic stem cell transplantation (HSCT) currently serves as a key treatment modality in a number of diseases including but not limited to hematological malignancies. The degree of HLA matching is considered important in the setting of HSCT. However, the availability of HLA-identical sibling donors is limited to about one-third of allogeneic transplant candidates. Therefore, other sources of stem cells including from umbilical cord or HLA-haploidentical family members (alternative donor sources) are being increasingly used. The level of HLA mismatch varies in these types of transplants, being highest in haploidentical transplants. Many transplant candidates, especially multiparous women are HLA allosensitized and the published literature reports HLA donor-specific antibody (DSA) rates from a low of 3% to a high of 24%. An increasing volume of outcomes data in alternative donor allogeneic HSCT patients and animal models suggest that engraftment failure rates are higher in recipients with HLA DSA.

Current management/treatment

Current strategies are aimed at identifying and defining HLA antibodies present in the recipient and to use this information to avoid selection of allogeneic donors with cognate antigens. As detailed above, however, not all recipients will have a donor without a cognate match. Based on numerous recent findings that transplants with HLA DSA fare worse than those without, several groups have utilized approaches including TPE, IA, IVIG, rituximab, and bortezomib to address elevated levels of HLA antibodies. The number of reports with the use of TPE/IA is limited (<30). The largest study of nine patients (Gladstone, 2013) used a protocol that included tacrolimus, mycophenolate mofetil, TPE, and IVIG, modeled on commonly utilized desensitization protocols in the area of incompatible renal transplant desensitization. In one case report, platelet transfusions from the HSCT donor (expressing DSA-cognate HLA Class I antigens) along with rituximab was performed to successfully decrease DSA levels and resulted in successful engraftment. This approach needs further study.

Rationale for therapeutic apheresis

Due to the now recognized role of DSA in engraftment failure, elimination/reduction of these antibodies peritransplant may result in improved outcomes. The limited case reports/series utilizing desensitization (primarily using TPE and another modality such as IVIG, rituximab or bortezomib) suggest that after adequate desensitization, engraftment successfully occurs in the vast majority of desensitized patients. It is believed that long-term chimerism may induce B-cell and T-cell tolerance that in turn results in continued decrease in HLA DSA levels contributing to long-term durability of these transplants. In the largest case series on desensitization in HSCT candidates with HLA DSA (Gladstone, 2013), the desensitization protocol included alternate-day, single volume TPE followed by low dose (100 mg/kg) CMV hyper-immmune IVIG. Treatment also included tacrolimus and mycophenolate mofetil during the desensitization regimen and bortezomib ∼3.5 months prior to desensitization. Using this protocol, DSA levels were decreased in all patients treated (9) with a mean reduction in DSA of 68.1%. Eight of the nine patients' DSA were below levels typically associated with positive flow cytometric crossmatches and these eight patients underwent HSCT. All patients engrafted successfully. Although it is unclear whether the 100% engraftment rate was primarily due to the effective desensitization protocol, this rate compares very favorably with primary engraftment failure rates of 75% in such patients. Additional, larger studies are warranted to fully establish the impact of these desensitization regimens on engraftment in DSA-positive allogeneic HSCTs.

Technical notes

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

Duration and discontinuation/number of procedures

The estimated number of TPE treatments is based on baseline DSA levels correlated with flow cytometric or complement-dependent cytotoxic crossmatch assays. In the largest case series (Gladstone, 2013) TPE was not performed during pretransplant conditioning or with post-transplant cyclophosphamide, but implemented before conditioning with one additional treatment on the day before graft infusion. Flow crossmatch positive patients received 4–5 treatments and complement-dependent cytotoxic crossmatch positive patients received additional treatments. In addition, patients with DSA rebound may require additional TPE treatments that are performed in the post-transplant phase.

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HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS; HEMOPHAGOCYTIC SYNDROME; MACROPHAGE ACTIVATING SYNDROME

Incidence: 1/800,000/yr (children: 1/1,000,000/yr)		Procedure	Recommendation	Category
		TPE	Grade 2C	III
No. of reported patients: < 100	RCT	CT	CS	CR
	0	1(23)	2(8)	4(4)

Description of the disease

Hemophagocytic syndrome (HS) or hemophagocytic lymphohistiocytosis (HLH) is an immune-mediated life-threatening disease. It is caused by impaired natural killer and cytotoxic T-cell function, which can be either primary (genetic, familial histolymphohistiocytosis [FHLH]) or secondary (reactive) after viral (EBV, CMV, H1N1, H5N1, parvovirus B19, influenza), bacterial (Tuberculosis, *Rickettsia* spp., *Staphylococcus* spp., *E. coli*), or fungal and parasitic (Histoplasma, plasmodium, toxoplasma, Pneumocystis) infections, cancer, vaccinations, surgery, gravidity, or autoimmune diseases (macrophage activating syndrome [MAS] in rheumatic disease). This results in an acute cytokine storm triggering an avalanche of hyperinflammation with a severe sepsis-like clinical picture. This hyperinflammation leads to a life threatening clinical picture with disseminated intravascular coagulopathy (DIC), organ failure, pancytopenia, systemic immune response syndrome (SIRS), and consecutively death, if untreated, in a few weeks. The diagnosis should be suspected in patients presenting with unexplainable, continuous high fever, and evidence of multiple organ involvement. The laboratory and clinical finding are not pathognomonic alone for HS, therefore diagnostic guideline from the Histiocyte Society are widely used. According to these, HLH is defined by the presence of at least five of the following criteria: (1) fever, (2) splenomegaly, (3) bicytopenia, (4) hypertriglyceridemia and/or hypofibrinogenemia, (5) infiltration with lymphocytes and histiocytes of, and hemophagocytosis in bone marrow, spleen, lymph nodes, or liver, (6) low/absent NK cell activity, (7) hyperferritinemia, and (8) high-soluble interleukin-2 receptor (CD25) levels. Molecular diagnoses consistent with FHLH are PRF1, UNC13D, STXBP1, RAB27A, STX11, SH2D1A, or XIAP.

Current management/treatment

The basis of treatment of HS are supportive intensive care according to the standards for similar life threatening diseases, the elimination of the trigger (for example, rituximab in EBV associated HS after HSCT) and the suppression of inflammatory response and cell proliferation or both with immunsuppressive and cytotoxic drugs (cyclosporin, corticoids, etoposide, IVIG, alemtuzumab). For l FHLH in pediatric patients HSCT is a curative option after immunsupressive therapy with corticoids, cyclosporin, etoposide. No RCTs are available wich investigate the best therapy according to the underlying trigger. Only retrospective trials are available, showing a good treatment response of secondary HS with corticoids and IVIG alone, and/or in combination with etoposide, cyclosporin, and alemtuzumab. In life threatening situations with uncontrolled hemorrhage and infections, risk due to DIC and granulocyto- and thrombocytopenia arises. Plasma, activated recombinant FVII, and cytokines (G-CSF) are widely used. Extracorporeal treatments like hemofiltration, dialysis, and TPE are also part of the supportive care to stabilize the organ function.

Rationale for therapeutic apheresis

The rational for TPE are organ failure, especially hepatic organ failure, or suppression of the hyperinflammatory syndrome, the excess of cytokines ("cytokine storm") and the coagulopathy. The use of TPE is not supported in large controlled trials. In children one CT was performed. Twenty-three children with hyperferritinemia and secondary HLH/sepsis/MODS/MAS were enrolled (median number of organ failures per patient was 5). The study demonstrated that use of TPE and methyl prednisolone or IVIG therapy ($n = 17$, survival 100%) was associated with improved survival compared to TPE and dexamethasone and/or cyclosporine and/or etoposide ($n = 6$, survival 50%) ($P = 0.002$). In a recent review (Ramos-Casels, 2014) of adult HS CRs and CSs were summarize and showed in patients with cancer, infection, and autoimmune disease, where TPE was used, had a survival rate of nearly 77% (20/26; survival of patients with cancer 9/10, autoimmune disease 6/8, infection 5/7, idiopathic 0/1). In one case with TTP, TPE was accused to aggravate the HLH. TPE demonstrated a promising performance which has to be proven by RCTs.

Technical notes

Filtration systems and centrifugal systems were described. There is no clear advantage of either technique.

Volume treated: 1–1.5–2 TPV	**Frequency**: every day depending on the secondary therapeutic goals
Replacement fluid: Albumin, plasma	

Duration and discontinuation/number of procedures

There is no clear demonstration of a definitive schedule used. TPE should be used according to intensive care practice depending on the underlying complication and morbidity.

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HENOCH–SCHÖNLEIN PURPURA

Incidence: 13.5 to 22.1/100,000 with 1% developing RPGN	**Indication**	**Procedure**	**Recommendation**	**Category**
	Crescentic	TPE	Grade 2C	III
	Severe extrarenal manifestations	TPE	Grade 2C	III
No. 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; 95% of HSP cases occur 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; IgA deposits within the mesangium of the glomerulus producing lesions ranging from mesangial proliferation to crescent formation and RPGN or crescentic glomerulonephritis, see Appendix and fact sheets on immune-complex rapidly progressive glomerulonephritis. IgG autoantibodies directed at mesangial antigens may also play a role in pathogenesis. Necrotizing vasculitis leads to organ dysfunction or hemorrhage in other organs.

In adults, the clinical presentation is more severe and outcomes are worse. 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. In adults, the presence of interstitial fibrosis and glomerulosclerosis on kidney biopsy 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 supportive care including hydration, rest, and pain control. In patients with severe kidney involvement (i.e., RPGN or crescentic glomerulonephritis) or severe symptoms of vasculitis, treatment can also include 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, 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 to 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. Double filtration plasmapheresis 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.

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As of August 31, 2015, 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.

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HEPARIN-INDUCED THROMBOCYTOPENIA AND THROMBOSIS

Incidence: 0.2–5% of patients exposed to heparin	Indication	Procedure	Recommendation	Category
	Pre-CPB	TPE	Grade 2C	III
	Thrombosis	TPE	Grade 2C	III
No. of reported patients: < 100	**RCT**	**CT**	**CS**	**CR**
Pre-CPB	0	0	1(11)	5(6)
Thrombosis	0	0	2(48)	6(6)

CPB = cardiopulmonary bypass.

Description of the disease

Heparin-induced thrombocytopenia and thrombosis (HIT/HITT) is a major cause of morbidity and mortality in patients receiving heparin. HIT causes thrombocytopenia classically beginning 5–10 days of the immunizing exposure, although individuals with a recent exposure to heparin (generally, within the preceding 100 days) may rapidly develop thrombocytopenia (within 24 h) upon heparin re-exposure. Antibodies specific for complexes of platelet factor 4 (PF4) and heparin are a hallmark of HIT. Delayed-onset HIT, i.e., HIT that begins or worsens after stopping heparin, often is recognized because of thrombosis, and is also associated with a higher frequency of overt disseminated intravascular coagulation and risk of microvascular thrombosis. There is also recent recognition of another severe type of HIT referred to as spontaneous HIT where the clinical course includes thrombocytopenia associated with thrombosis, and serological findings include strong-positive testing in both anti-PF4/heparin immunoassay and platelet activation assay but the patient has not had any known exposure to heparin within the preceding weeks.

Current management/treatment

After recognizing a possible case of HIT, all heparin, including that given by "flushes," should be discontinued. Because of the continued risk of thrombosis after heparin cessation, all patients with confirmed or strongly-suspected HIT should be therapeutically anticoagulated with an alternative agent, typically a direct thrombin inhibitor (DTI), fondaparinux (off-label use), or danaparoid (off-label use). HIT management is particularly challenging in two scenarios: (1) Worsening or new thrombosis with life- or limb-threatening complications despite optimal management with non-heparin anticoagulants; and (2) persistent platelet-activating HIT antibodies in patients who need emergent/urgent cardiac surgery on CPB. The standard anticoagulant used with CPB is unfractionated heparin (UFH) due to its longstanding track record of use in this setting, its short half-life, and immediate reversibility; however, heparin is typically contraindicated in patients with acute or sub-acute (persistent platelet-activating HIT antibodies even without thrombocytopenia) HIT. In this setting, consensus guidelines recommend the use of bivalirudin over other non-heparin anticoagulants and over heparin plus antiplatelet agents. The major concern with DTI use in CPB is severe bleeding due to lack of reversibility.

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. In the setting of urgent need for surgery with CPB during acute or subacute HIT, pre-surgical TPE may be considered prior to UFH-based CPB as an alternative to using a DTI during bypass. In the largest retrospective series on the use of TPE in the pre-CPB setting, a single TPE treatment reduced HIT antibody titers (as measured by PF4-polyvinylsulfonate immunoassay) 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 nine patients developed clinical HIT after CPB with UFH; however, one patient developed an ischemic foot 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 severe thrombosis, 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; $n = 7$). Reduction in HIT antibody levels was quantified by optical density in a PF4-heparin immunoassay in some patients and with heparin-induced platelet aggregation (HIPA) in others. TPE treatment resulted in a negative HIPA test in >75% 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 longer/higher in the late group.

Technical notes

Recent data suggests that after TPE treatments, there is a rapid decline in platelet-activating HIT antibodies (as determined by the serotonin release assay (SRA) in a study by Warkentin, 2015) even in the presence of strongly reactive antibodies detected by HIT immunoassays. Platelet activation assays are thought to measure clinically relevant antibodies, thus such assays may be more helpful in guiding TPE treatment in patients with HIT.

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 been used preoperatively until HIT antibody titers become negative by the testing method used. It is recommended that a platelet activation assay be used to guide treatment. In the setting of thrombosis, the number of procedures performed has been heterogeneous (1–5) and guided by clinical response (e.g. resolution of thrombosis-related tissue ischemia)/reduction in HIT antibodies levels.

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HEREDITARY HEMOCHROMATOSIS

Incidence: 1.4/100,000/yr		Procedure Erythrocytapheresis	Recommendation Grade 1B	Category I
# of reported patients: >300	RCT 2(100)	CT 2(98)	CS 13(122)	CR 1(1)

Description of the disease

Hereditary hemochromatosis (HH) 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 homozygous for a single missense mutation in *HFE* on chromosome 6p21 that results in substitution of cysteine with tyrosine at amino acid 282 (C282Y), known as Type I HH. The prevalence of Type I HH is $\sim$1:200 among Caucasians. Abnormalities of *HFE* result in abnormal iron sensing in the deep crypt cells of gut epithelium and thus inappropriate iron uptake despite abundant iron stores in the body. Other genetic mutations coding for hemojuvelin (*HFE2*, type IIA), hepcidin (*HAMP*, type IIB), transferrin receptors (*TFR2*, type III), or ferroportin (*SLC40A1*, type IV), have been described in rare families with non-HFE HH. In HH, 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 70% of homozygotes developing clinical manifestations of disease, 10% any end-organ complications, and 0.04% full-blown complications.

Current management/treatment

Because HH is a disease of iron overload, iron removal by therapeutic phlebotomy has been the mainstay of treatment both to remove iron and to increase erythropoiesis to mobilize stored iron. Phlebotomy is recommended when serum ferritin is elevated even in the absence of symptoms or signs of end-organ damage. Typically, one whole blood unit 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 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 situations where 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

A RCT (Rombout-Sestrienkova, 2012) compared biweekly erythrocytapheresis of 350–800 mL of RBCs to a minimum post-procedure Hct of $\geq$30% with weekly phlebotomy of 500 mL among 38 patients with newly diagnosed HFE HH. The mean number of procedures and treatment duration to achieve ferritin of ≤ 50 ng/mL were 9 and 20 weeks for the erythrocytapheresis group versus 27 and 34 weeks ($p < 0.001$ and $p < 0.002$), respectively, for the phlebotomy group. No difference in adverse events and no significant difference in total treatment costs were observed (the higher cost of erythrocytapheresis was offset by a significant reduction in lost work productivity due to phlebotomy visits). A second RCT (Sundic, 2014) enrolled 30 patients for biweekly apheresis (400 mL) and 32 patients for weekly whole blood phlebotomy (450 mL). Time to normalization (50 ng/mL) of ferritin was equivalent; cost for apheresis was 3$\times$ higher. A CT using another apheresis platform removed 300–550 mL of RBCs in patients with Hct $>$37%, weight > 50 kg, and age 18–65 years with mean reduction of 405 mg of iron per procedure. Thus cost and ability to rapidly lower ferritin and iron stores differ by the ability of RBC reduction per apheresis, which varies by apheresis technology, and patient's weight and height.

Technical notes

The volume removed and pre-procedure Hct vary by height, bodyweight, and gender. The actual volume of erythrocytes to be removed (VR) with each procedure can be calculated as:

$$VR = [(\text{starting HCT} - \text{target HCT}) \div 79] \times [\text{blood volume (ml/kg)} \times \text{body weight (kg)}]$$

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 pre-procedure Hct $\geq$ 30–36% and post-procedure 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.

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HYPERLEUKOCYTOSIS

Incidence: AML: WBC >100 × 109/L: 5–18% in adults, 12–18% in children; ALL: WBC >400 × 109/L: ≤3%	Indication	Procedure	Recommendation	Category
	Symptomatic	Leukocytapheresis	Grade 1B	II
	Prophylactic or secondary	Leukocytapheresis	Grade 2C	III
No. of reported patients: >300	**RCT**	**CT**	**CS**	**CR**
AML	0	6(437)	16(473)	14(16)
ALL	0	3(366)	6(57)	2(2)

ALL = acute lympoblastic leukemia; AML = acute myeloid leukemia.

Description of the disease

Hyperleukocytosis is defined as a circulating white blood cell (WBC) or leukemic blast cell count >100 × 10^9/L. Hyperleukocytosis with acute myeloid leukemia (AML) (WBC counts >100 × 10^9/L) and acute lymphoblastic leukemia (ALL) (WBC counts >400 × 10^9/L) may be associated with tumor lysis syndrome (TLS), disseminated intravascular coagulopathy (DIC), leukostasis, and worse prognosis. In AML, hyperleukocytosis is often associated with AML FAB types M4 and M5 (blast counts <50 × 10^9/L). Leukostasis refers to end-organ complications due to microvascular leukoaggregates, hyperviscosity, tissue ischemia, infarction, and hemorrhage. 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. CNS manifestations include confusion, somnolence, dizziness, headache, delirium, coma, and parenchymal hemorrhage. Pulmonary complications include hypoxemia, diffuse alveolar hemorrhage, and respiratory failure. 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. Leukostasis complications with other leukemias are rare but may occur with chronic myelomonocytic leukemia and WBC counts >100 × 10^9/L with high LDH. Priapism may occur with chronic phase chronic myeloid leukemia and WBC counts >500 × 10^9/L.

Current management/treatment

Definitive treatment of hyperleukocytosis involves induction chemotherapy with aggressive supportive care. Hydroxyurea and/or cytarabine are useful temporizing cytoreductive agents for AML. Rapid cytoreduction is indicated to treat symptomatic leukostasis. 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 remains poorly defined.

Leukocytapheresis has been performed in patients with acute promyelocytic leukemia (APL)/FAB type M3 with no improvement in outcome compared to patients receiving remission induction chemotherapy. One study found that leukocytapheresis in APL may have been a trigger for "catastrophic occurrences" contributing to early mortality (Vahdat, 1994). Central catheter placement and invasive procedures are generally avoided in APL patients during remission induction due to high risk of hemorrhage.

Rationale for therapeutic apheresis

Rapid reduction of the intravascular leukemic cellular burden by leukocytapheresis improves tissue perfusion with evidence of rapid reversal of pulmonary and CNS manifestations with leukocytapheresis. Even though leukapheresis can reduce WBC significantly faster than chemotherapy alone, some studies have demonstrated higher earlier death rate. This could however be in part due to higher risk of the patients undergoing leukapheresis. Improvement may not be observed, particularly, if severe end-organ injury or hemorrhage has already occurred.

Multiple retrospective cohort studies of AML with hyperleukocytosis suggest that prophylactic leukocytapheresis (asymptomatic) can reduce the rate of early death (≤3 weeks into treatment); although there is no impact on later mortality and overall or long-term survival. Others studies have reported no benefit and raised concerns that leukocytapheresis might delay start of induction chemotherapy. A more recent systematic review and meta-analysis in patients with AML and initial WBC≥100 × 10^9 revealed that early mortality related to hyperleukocytosis in AML was not influenced by the use of leukapheresis. Limitations to the primary studies include the retrospective, observational nature of the publications, the number of which was small and having moderate to high risk of confounding bias. Leukapheresis may still have a therapeutic role in patients presenting with severe leukocytosis or end-organ damage from leukostasis. Chemotherapy should not be postponed and is required to prevent rapid reaccumulation of circulating blasts.

Among children and adults with ALL, clinical symptoms of leukostasis develop in <10% at WBC counts <400 × 10^9/L. Therefore, prophylactic leukocytapheresis offers no advantage over aggressive induction chemotherapy and supportive care, including those with TLS. Pulmonary and CNS complications develop in >50% of children with WBC counts ≥400 × 10^9/L, suggesting that prophylactic leukocytapheresis might be beneficial in that setting.

Technical notes

A single leukocytapheresis can reduce the WBC count by 30–60%. Erythrocyte sedimenting agents (hydroxyethyl starch) are not required for AML or ALL. RBC priming may be employed for selected adults with severe anemia; however, RBCs should be avoided in small children with hyperviscosity. Utilize replacement fluid to ensure at least a net even ending fluid balance of ±15% of TBV.

Volume treated: 1.5–2 TBV	**Frequency**: Daily
Replacement fluid: Crystalloid, albumin and/or plasma	

Duration and discontinuation/number of procedures

For AML patients with leukostasis complications, discontinue when the blast cell count is <50–100 × 10^9/L and clinical manifestations resolved. For prophylaxis of AML patients, discontinue treatments when the blast cell count is <100 × 10^9/L (closely monitor patients with M4 and M5 subtypes). For ALL patients with leukostasis complications, discontinue when the blast cell count is <400 × 10^9/L and clinical manifestations resolved. For prophylaxis of ALL patients, discontinue treatment when the blast cell count is <400 × 10^9/L.

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HYPERTRIGLYCERIDEMIC PANCREATITIS

Incidence: 18/100,000/yr		Procedure TPE	Recommendation Grade 2C	Category III
No. of reported patients: 100–300	RCT 0	CT 1(20)	CS 16(235)	CR 38(39)

Description of the disease

Hypertriglyceridemia (HTG) results from increased production and/or decreased catabolism of triglycerides (TG). Primary causes include familial hypertriglyceridemia (FHTG), familial combined hyperlipidemia (FCHL), and familial dysbetalipoproteinemia (Type III hyperlipidemia). Secondary causes include diabetes mellitus (DM), chronic renal failure, nephrotic syndrome, hypothyroidism, pregnancy, inactivity, high-carbohydrate diets, excess alcohol intake, and medications (corticosteroids, bile acid sequestrants, anti-hypertensives, estrogens, retinoids, diuretics, and antiretrovirals). Extreme TG elevations are seen in patients homozygous for known mutations as well as when secondary causes are superimposed on inborn errors in TG metabolism such as deficiencies of lipoprotein lipase (LpL) or apolipoprotein C-II (apoC-II). Acute pancreatitis may develop when TG levels are >500–1,000 mg/dL and mortality from this complication may be upto 30%.

Current management/treatment

Treatment for HTG includes dietary restriction and lipid lowering agent administration (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. Insulin activates lipoprotein lipase and may be used when DM is present. Heparin releases LpL from endothelial stores enhancing TG clearance but may exacerbate hemorrhage into the pancreatic bed in the setting of pancreatitis and, therefore, its use is controversial.

Rationale for therapeutic apheresis

TPE can significantly decrease TG levels, reduce inflammatory cytokines, and potentially replace deficient LpL or apolipoproteins when plasma is used as the replacement fluid. Multiple case reports, series, and one nonrandomized controlled trial have examined the use of TPE to treat acute pancreatitis due to HTG. 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. Reductions in TG levels of 49–80% have been reported following a single TPE procedure. Treatment goals are to reduce TG levels to < 500–1,000 mg/dL. It is important to note that while TPE can rapidly decrease the TG level, its effect is transient; adequate lipid lowering treatment is essential to achieve a persistent effect. Since fibrate, the mainstay of medical therapy for HTG has been associated with teratogenic effects, TPE has also been successfully used as a treatment strategy for acute pancreatitis due to HTG during pregnancy (Basar, 2013).

A single published trial with historic control found no difference between standard therapy and TPE ($n = 10$) versus standard therapy alone ($n = 19$) in patients with severe acute pancreatitis with regard to mortality, systemic complications, and local complications in patients with severe pancreatitis (Chen, 2004). 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. A more recent case series describing 103 patients found that TPE reduced triglycerides by twice that observed with conservative management but the TG level at presentation did not correlate with clinical severity as measured by APACHE II score. There was no difference in mortality between early (< 36 h after onset of pain) and late initiation of TPE (Gubensek, 2014).

Several series have reported on the use of maintenance TPE to maintain TG levels < 150 mg/dL to prevent further episodes of pancreatitis.

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. A recent large case series found that patients who underwent TPE using citrate anticoagulation during TPE had a significantly lower mortality than the group with heparin anticoagulation (1% vs. 11%, $P = 0.04$) (Gubensek, 2014).

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 replacement fluids have been reported.

Treatment has usually been implemented early in the course of 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
Replacement fluid: Albumin, plasma

Frequency: Therapeutic: daily for 1–3 days depending upon patient course and TG level; Prophylactic: every 2–4 weeks to maintain TG level < 150 mg/dL

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.

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HYPERVISCOSITY IN MONOCLONAL GAMMOPATHIES

Incidence: 5/1,000,000/yr	Indication	Procedure	Recommendation	Category
	Symptomatic	TPE	Grade 1B	I
	Prophylaxis for rituximab	TPE	Grade1C	I

No. of reported patients:>300	RCT	CT	CS	CR
Symptomatic	0	3(46)	19(263)	NA
Prophylaxis for rituximab	0	0	3(45)	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 such as that of the eye and other mucosal surfaces. Hyperviscosity syndrome (HVS) refers to the clinical sequelae caused by the altered physiology related to plasma hyperviscous states, most typically seen in Waldenström's macroglobulinemia (WM) associated with monoclonal IgM or, less frequently, with multiple myeloma (MM) associated with monoclonal IgA or IgG3. Signs and symptoms of HVS include headache, dizziness, 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, peripheral polyneuropathy, and anorexia. When the IgM protein associated with WM exceeds a concentration of 4 g/dL, the relative plasma viscosity can exceed 4 centipoise (cp; relative to water: normal range, 1.4–1.8 cp) and HVS can occur. Serum viscosity measurement does not consistently correlate with clinical symptoms among individual patients, however, the viscosity level at which the syndrome appears is generally reproducible within the same patient (symptomatic threshold). Most patients will be symptomatic at levels of 6–7 cp. HVS occurs in MM with 6–7 g/dL of monoclonal IgA or 4 g/dL of monoclonal IgG3 in the plasma.

Current management/treatment

The current standard of care for HVS is removal of the paraprotein by TPE. Early diagnosis, which can usually be made from the funduscopic examination, is crucial to prevent further progression. TPE should be carried out as soon as the diagnosis is made. TPE does not affect the underlying disease process, thus systemic chemotherapy or immunotherapy should be initiated soon after TPE as serum IgM levels will return to baseline in 4–5 weeks. Patients with WM are usually managed using a risk-adapted approach. Patients with constitutional symptoms, hematological compromise, and bulky disease should be considered for chemotherapy +/− immunotherapy. Frontline treatments include alkylators (bendamustine and cyclophosphamide), proteasome inhibitors (bortezomib and carfilzomib), nucleoside analogs (fludarabine and cladribine), and ibrutinib. The addition of rituximab to alkylating agent-based combinations has further increased patient response rates and reduced WM-related mortality, independently of other prognostic factors. For patients with preserved hematological function and IgM MGUS (<10% lymphoplasmacytic marrow infiltration) watchful waiting is most appropriate. Rituximab may be used alone as first-line treatment in low-risk patients with mild anemia, thrombocytopenia, and/or peripheral neuropathy, and/or hemolytic anemia uncontrolled with corticosteroids. Pregnant patients unable to receive systemic therapy may be candidates for TPE.

Rationale for therapeutic apheresis

TPE has successfully used since the late 1950s and has shown to promptly reverse retinopathy and other clinical manifestations of HVS. IgM is 80% intravascular and serum viscosity rises steeply with increasing IgM levels. Thus, a relatively small reduction in IgM concentration has a significant effect on lowering serum viscosity. TPE reduces viscosity 20–30% per treatment.

A transient increase in IgM levels, after rituximab therapy (flares) has been reported in 30–70% of patients within 4 weeks of treatment initiation. TPE should be considered before giving rituximab if serum viscosity > 3.5 cp or IgM level > 4 g/dL. Acquired von Willebrand disease has been reported in WM; low von Willebrand factor levels are associated with higher concentration of IgM and hyperviscosity. Whether patients with IgM proteins having autoantibody activity and consequent immune-mediated organ damage should receive more aggressive TPE is unknown.

Technical notes

Conventional calculations of plasma volume based on weight and hematocrit are inaccurate in M-protein disorders because of plasma volume expansion. Relatively small exchange volumes (1–1.5 TPV) per procedure are effective since plasma viscosity falls rapidly as M-proteins are removed. Cascade filtration and membrane filtration techniques have been described but centrifugation apheresis has shown to be more efficient than cascade filtration in removing M-protein.

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

Duration and discontinuation/number of procedures

Daily TPE until acute symptoms abate (generally 1–3 procedures). Clinical monitoring, viscosity as well as IgM levels are recommended during treatment to determine whether subsequent TPE procedures are necessary.

Retinal changes in otherwise asymptomatic patients with WM respond dramatically to single plasma exchange with marked or complete reversal of the abnormal examination findings. When patients are maintained at a level under their symptomatic threshold, clinical manifestations of the syndrome usually are prevented. A maintenance schedule of TPE every 1–4 weeks based on clinical symptoms or retinal changes may be employed to maintain clinical stability pending a salutary effect of chemotherapy +/− immunotherapy.

Prophylactic TPE is performed to lower IgM to < 4 g/dL prior to Rituximab therapy.

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IMMUNE THROMBOCYTOPENIA

Incidence: Adult: 38/1,000,000/year; Child: 46/1,000,000/year	Indication	Procedure	Recommendation	Category
	Refractory	TPE	Grade 2C	III
	Refractory	IA	Grade 2C	III

No. of reported patients: 100–300	RCT	CT	CS	CR
TPE	0	0	4(30)	2(2)
IA	0	0	6(136)	0

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. In the majority of childhood ITP, no treatment is required; however, 20% will not go into an immediate remission and will continue to be thrombocytopenic. Adult ITP, which predominantly affects women aged 18–40 years, 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 systemic lupus erythematosus, 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 $<30 \times 10^9$/L, in patients younger than 40, 40–60, and >60 years old, this risk is 0.4%, 1.2%, and 13% per patient year, respectively. By a consensus conference, ITP was classified into: newly diagnosed ITP (0–3 months), persistent ITP (3–12 months), chronic ITP (lasting more than 12 months), and refractory ITP (refractory to standard treatment).

Current management/treatment

Therapy is generally not indicated when the 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 a single dose of anti-Rh D in RhD positive patients may be substituted for prednisone for rapid response. If thrombocytopenia persists or recurs, splenectomy is often preferred as second-line therapy but thrombopoeitin receptor agonists. Splenectomy is deferred for one year in children to avoid overwhelming postsplenectomy infection and to allow for spontaneous remission. Rituximab, and salvage therapies such as danazol, vinca alkaloids, cyclophosphamide, azathioprine, and cyclosporine, may be considered based on bleeding, clinical risks, and patient-specific considerations.

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. IA may be considered in patients with refractory ITP, with life-threatening bleeding or in whom splenectomy is contraindicated. Columns have a high affinity for IgG and IgG-containing circulating immune complexes that can be selectively removed from the patient's plasma. 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 $50–100 \times 10^9$/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. The staphyloccal protein A columns was removed from market in 2006. Recent studies with IA used other commercially available systems. Most recent studies used TPE and IA in combination with other treatment modalities (glucocorticoids, IVIG) or as preparative treatment to achieve a splenectomy in severely and refractory thrombocytopenic patients.

Technical notes

Using Staphylococcal protein A silica, the procedure can be done either online 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: 2–4 TPV	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 6 treatments.

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IMMUNOGLOBULIN A NEPHROPATHY

Incidence: 4/100,000 with 10% developing RPGN	Indication	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 nephropathy is the most common form of glomerulonephritis in the developed world, particularly in Asians and Caucasians. It is frequently asymptomatic with a benign course (no severe kidney damage) but there are reports of slow progression to end stage renal disease (ESRD) over 20 to 25 years in up to 50% of patients (chronic progressive) and, less commonly, the aggressive crescentic form can occur. Histologically, glomerular deposits of IgA characterize IgA nephropathy. Roughly >10% of patients can present as rapidly progressive crescentic glomerulonephritis (see immune-complex RPGN fact sheet). When there are symptoms, the classic presentation for the disease is gross hematuria occurring shortly after an upper respiratory infection (synpharyngitic) or, when asymptomatic, discovery of microscopic hematuria with or without proteinuria. Factors associated with disease progression are hypertension, persistent proteinuria >1,000 mg/day, and elevations in serum creatinine. The crescentic 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 pathologic IgA1, (2) IgG antibodies are generated toward this IgA1, (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 blood pressure control, control of proteinuria with ACE 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 for 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 and IgA immune complexes levels. 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 case series from previous decades have addressed the treatment of the rapidly progressive form. The majority of these patients were treated with TPE and concurrent corticosteroids and/or immunosuppressants with reported improvement in kidney function and decrease in serum IgA. 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. A controlled trial (Roccatello, 2000) 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 kidney 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 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

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

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.

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As of August 27, 2015, 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.

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INFLAMMATORY BOWEL DISEASE

Incidence: UC: 35–100/100,000; CD: 27–48/100,000	Indication	Procedure	Recommendation	Category
	UC	Adsorptive cytapheresis	Grade 1B[a]/2B[b]	III[a]/II[b]
	CD	Adsorptive cytapheresis	Grade 1B	III
	CD	ECP	Grade 2C	III

No. of reported patients: >300	RCT	CT	CS	CR
UC	12(724)	2(92)	23(1973)	NA
CD	2(258)	0	Cytapheresis: 5(125); ECP: 2(59)	NA

UC = ulcerative colitis; CD = Crohn's disease.

[a]The standard of care in US includes immunosuppression with TNFα blockade whereas bconventional therapy in Asia consists of steroids and amino-salicylates 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 gastrointestinal tract and are collectively known as inflammatory bowel disease (IBD). The phenotype of these disorders is variable, affecting predominately individuals in the third decade of life. 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 progressive tissue damage and lead to the debilitating clinical manifestations of IBD.

Current management/treatment

First-line therapies for IBD include anti-inflammatories, 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. Unfortunately, complications from chronic steroid administration include steroid resistance, dependency, and the sequelae of long-term steroid use. For those with refractory disease thiopurines, such as azathioprine and 6-mercaptopurine are used. In CD specifically, infliximab, monoclonal antibody to anti-tumor necrosis factor, may induce remission and has been FDA cleared for this purpose. Surgical intervention may be necessary in some patients.

Rationale for therapeutic apheresis

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 toward an immune modulatory phenotype. A recent meta-analysis synthesized the findings of nine randomized controlled trials examining granulocytapheresis using the Adacolumn to treat UC (Yoshino, 2014). This treatment was effective for achieving a clinical response in patients with active UC when compared to corticosteroids. Intensive therapy (>2 sessions per week) resulted in a higher remission rate when compared to patients treated weekly. However, one included RCT showed no difference in the remission rate when adsorptive cytapheresis was compared to sham treatment (Sands, 2008). A post hoc analysis of this study demonstrated that the treated subset of patients with microscopic erosions/ulcerations had a significantly higher remission rate when compared to the sham group (Kruis, 2015). Factors that may impact response to therapy in UC include disease activity level, duration, and response to corticosteroids.

Evidence supporting the use of adsorptive cytapheresis to treat CD is more limited. Although a few uncontrolled studies have demonstrated efficacy in the treatment of active CD, a recently published large RCT did not demonstrate any difference in remission rates when compared to sham treatment in patients with moderate to severe CD (Sands, 2013). Two uncontrolled case series have been published suggesting that ECP can promote remission for a proportion of patients with steroid and/or immunosuppressant intolerant CD. Further study is warranted to determine whether ECP is a viable treatment option for CD.

Technical notes

Two types of selective apheresis devices are the Cellsorba (Asahi Medical, Tokyo, Japan) which is a column containing cylindrical non-woven polyester fibers and, the Adacolumn (JIMRO, Japan) which contains cellulose acetate beads. Both require anticoagulation (heparin/ACD-A and heparin alone, respectively) to remove granulocytes and monocytes from venous whole blood by filtration/adhesion. For Cellsorba, venous whole blood is processed at 50 mL/min through the column for 60 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: 3000 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.

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LAMBERT–EATON MYASTHENIC SYNDROME

Incidence: 0.5/1,000,000		Procedure TPE	Recommendation Grade 2C	Category II
No. of reported patients: <100	**RCT** 0	**CT** 0	**CS** 6(37)	**CR** 5(6)

Description of the disease:

The Lambert–Eaton myasthenic syndrome (LEMS) is an autoimmune disorder of presynaptic neuromuscular transmission. Its classical clinical triad include: muscle weakness (most prominent in proximal muscles of the lower extremities), hyporeflexia, and autonomic dysfunction (e.g., dry mouth, constipation, and male impotence). In contrast to myasthenia gravis (MG), brain stem symptoms such as diplopia and dysarthria are uncommon. Approximately 60% of patients have small cell lung cancer (SCLC) that may not become radiographically apparent for 2–5 years after the onset of the neurological syndrome. Other cancers such as lymphoma and malignant thymoma have been reported in association with LEMS. LEMS is estimated to occur in 3–6% of patients with small cell lung cancer. Rapid onset and progression of symptoms over weeks or months should heighten suspicion of underlying malignancy. While SCLC-LEMS typically presents at the age ≥50 years with male predominance, non-tumor LEMS can be seen in all age groups with a peak between the ages of 35 and 60 and a female predominance. LEMS is very rare in children.

The diagnosis of LEMS is confirmed by the typical electrophysiological studies and the presence of autoantibodies directed at the P/Q type voltage-gated calcium channel (VGCC) of the nerve terminal (found in 85–90% of patients). The antibodies are believed to cause insufficient release of acetylcholine quanta by action potentials arriving at motor nerve terminals. Unlike MG, which is characterized by antibodies to the postsynaptic acetylcholine receptor, VGCC antibodies target the pre-synaptic structure. The antibody to VGCC is approaching 100% in SCLC-LEMS, and in 50% of non-tumor LEMS patients. 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 of acetylcholine-mediated neurotransmission to improve neurological function and immunosuppression to control production of the autoantibodies. 3,4-DAP (3,4-Diaminopyridine) is now considered 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 tend to be less effective given alone than they are in MG but can be combined with agents, such as guanidine hydrochloride, that act to enhance release of acetylcholine from the presynaptic nerve terminal.

In case of limited response to 3,4-DAP, immunosuppressive therapy must be considered. Studies have reported significant improvement following the combination treatment of prednisolone and azathioprine. 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 have suggested a benefit. In one series, 8 out 9 patients (Newsom-Davis, 1984) had increase in electromyographic muscle action potential ($P < 0.01$) while receiving TPE and immunosuppression. TPE produces relatively rapid, albeit temporary (~6 weeks), improvement in most LEMS patients. 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 to 15 daily TPE over 5–19 days to 8–10 TPE carried out at 5–7 day intervals. Most reports indicate an exchange volume of 1.25 plasma volumes. Of note: improvement may not be seen for 2 weeks or more after initiation of TPE. This may be due to the slower turnover of the presynaptic VGCC compared to the postsynaptic acetylcholine receptor.

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

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 upto 6 weeks in the absence of immunosuppressive therapy.

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LIPOPROTEIN (A) HYPERLIPOPROTEINEMIA

Incidence: Unknown		Procedure LDL apheresis	Recommendation Grade 1B	Category II
No. of reported patients: > 300	RCT 2(41)	CT 3(293)	CS 6(95)	CR 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 < 30 mg/dL (1.6 mmol/L) but levels can vary up to 1,000-fold between individuals. Lp(a) levels are genetically controlled. 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, which results in enhanced coagulation and inhibition of fibrinolysis, producing a prothrombotic state. Lp(a) 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 (CAD) and ischemic stroke. There is no recognized 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) ($< 10\%$) with negligible benefit to the patients with extreme elevations. Recently approved PCSK9 inhibitors are monoclonal antibodies that can significantly lower Lp(a) in patients with hypercholesterolemia, but the mechanism of this effect is unknown.

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 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 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) and significantly fewer cardiac events per patient per year after initiation of treatment. A randomized controlled trial of 21 patients with isolated Lp(a) and angiographically documented CAD 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 examined the acute effects of LDL apheresis in 20 patients with CAD 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 available LDL apheresis devices are all capable of removing Lp(a) with similar degrees of reduction. Please refer to the Appendix in the Introduction section for information on the different LDL cholesterol selective removal systems in use. There have been no reports of the use of TPE to treat elevations of Lp(a). 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, 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.

Guidelines for the use of LDL apheresis to treat elevated Lp(a) vary from country to country. The European Atherosclerosis Society Consensus Panel recommends the reduction of Lp(a) <50 mg/dL. The HEART-UK criteria for the use of LDL apheresis includes patients with progressive CAD, hypercholesterolemia, and Lp(a) > 60 mg/dL in whom LDL cholesterol remains elevated despite drug therapy. The German reimbursement guidelines permit LDL apheresis for patients with Lp(a) > 60 mg/dL and progressive CAD, even if the LDL-C is within normal range.

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) < 50 mg/dL (2.77 mmol/L).

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As of October 5, 2015, 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.

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LIVER TRANSPLANTATION

Incidence:	Indication	Procedure	Recommendation	Category
ABOi LDLT-Rare;	Desensitization, ABOi LD	TPE	Grade 1C	I
ABOi DDLT-Rare	Desensitization, ABOi DD[a]	TPE	Grade 2C	III
	AMR (ABOi & HLA)	TPE	Grade 2C	III
No. of reported patients: > 300	**RCT**	**CT**	**CS**	**CR**
Desensitization: ABOi LDLT	0	0	14(1184)	1(1)
Desensitization: ABOi DDLT	0	0	7(60)	9(9)
AMR	0	0	0	6(7)

ABOi = ABO-incompatible; AMR = antibody mediated rejection; DDLT = deceased donor; LD = liver donor. [a]TPE based desensitization is not indicated in the setting of group A-subtype (e.g. A_2) into group O DD.

Description of the disease

Due to a relative shortage of compatible organs for transplantation, ABO incompatible (ABOi) liver transplants are being more frequently performed. There is also increasing use of live donor liver transplantation, where a portion of donor's liver is transplanted into the recipient. 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 antibody-induced endothelial damage (A and B antigens are expressed on vascular endothelium). ABO antibody mediated severe liver injury is very well documented. Many recent publications including an expert panel report (O'Leary, 2014) on the impact of donor specific HLA antibodies on short- and long-term outcomes in liver transplantation suggests a potential role of HLA antibodies in mediating liver allograft injury, something that was previously not thought to occur.

Current management/treatment

There has been significant progress in the use of TPE perioperatively in ABOi deceased donor liver transplant (DDLT) and for preconditioning/antibody mediated rejection (AMR) treatment in ABOi live donor liver transplant (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 East Asia with patients being treated with rituximab, TPE, and hepatic infusion with prostaglandin E1 and methylprednisolone with good survival statistics. Intestinal perforation is one of the major risks associated with local intravascular infusion. Similar to the ABOi renal transplant setting, rituximab appears to be as effective as splenectomy in enabling ABOi LDLT. Individuals with the A_2 blood group have reduced expression of the A antigen on endothelium (and RBCs). A large retrospective series on DDLT suggests that A_2 into O transplants is safe with similar graft and overall survival relative to ABO-compatible DDLT. Liver humoral rejection due to donor-specific HLA antibodies was a controversial entity previously, however, multiple studies suggest that a number of liver pathologic correlates including hyperacute rejection, "steroid-resistant" rejection, idiopathic/accelerated fibrosis and biliary strictures, have been associated with HLA donor-specific antibodies in liver transplantation.

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 both ABO and HLA antibodies. An increasing number of retrospective studies suggest that TPE in combination with enhanced immunosuppression may be effective in reversing humoral rejection of the liver allograft. Specific diagnostic criteria to calculate a chronic AMR (cAMR) score has recently been proposed and appears to identify liver allograft recipients at highest risk for allograft loss (O'Leary, 2015).

Technical notes

The replacement fluid for TPE is plasma, or albumin and plasma (plasma should be compatible with both the recipient and donor organ ABO type in ABOi transplants). Plasma use is frequent in this setting due to underlying coagulopathy secondary to liver failure. Typical anticoagulation used is ACD-A, however heparin-based anticoagulation may be considered if liver function is too poor to metabolize ACD-A.

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 ABO antibody titer to less than a critical threshold prior to taking the patient to ABOi liver transplant. It is important to note that this critical titer will need to be determined by each program undertaking 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 with TPE. Unlike in ABOi renal transplantation, the predictive value of post-transplant titers is less well established. Patients should be monitored closely for graft dysfunction before discontinuation of TPE. For treatment of liver rejection, TPE is usually used until improvement in liver function (liver enzymes/bilirubin).

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LUNG TRANSPLANTATION

Incidence: Bronchiolitis obliterans syndrome: 25% at 2.5 yr and 50% at 5.6 yr; AMR/Desensitization: Infrequent	**Indication**	**Procedure**	**Recommendation**	**Category**
	BOS	ECP	Grade 1C	II
	AMR	TPE	Grade 2C	III
	Desensitization	TPE	Grade 2C	III
No. of reported patients: >300	**RCT**	**CT**	**CS**	**CR**
BOS	0	0	10(348)	5(5)
AMR	0	0	4(39)	3(4)
Desensitization	0	0	1(8)	0

AMR = antibody mediated rejection; BOS= bronchiolitis obliterans syndrome

Description of the disease

Approximately half of lung transplant patients develop bronchiolitis obliterans syndrome (BOS) within 5 years of transplant. Chronic rejection is manifested as BOS, a pathological process that affects small airways. BOS can be difficult to diagnose by transbronchial biopsy and thus the diagnosis is made based on graft deterioration due to persistent airflow obstruction instead of histologic confirmation. The diagnosis of BOS is defined by a sustained (> 3 week) decline in expiratory flow rates, provided that alternative causes of pulmonary dysfunction have been excluded. According to the International Society for Heart and Lung Transplantation (ISHLT) classification used widely to define the severity of BOS, Category 0 refers to no significant abnormality and FEV_1 >90% of best postoperative value, potential BOS (0-p) is defined as 81–90% of FEV_1, BOS Category I 66–80% of FEV_1, Category II 51–65% of FEV_1, and Category III 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 and rate of decline of FEV_1 are highly variable. Single lung transplantation conveys a higher risk for earlier onset of BOS compared with bilateral transplantation, and unfavorable outcome appears to be associated with rapid onset, female gender, and pretransplant idiopathic pulmonary fibrosis. Whether antibody mediated rejection (AMR) after lung transplantation exists as an entity has been the subject of debate, however, increasingly, 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.

Current management/treatment

At the time of transplantation, many 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 calcineurin inhibitor (cyclosporine or tacrolimus), antimetabolite (azathioprine or mycophenolate mofetil), and steroids. Short courses of intravenously pulsed corticosteroids, followed by a temporary increase in maintenance doses for few weeks, are the preferred treatment for uncomplicated acute rejection. The initial treatment of BOS usually consists of repeated pulses of high-dose methylprednisolone. For patients with unresponsive BOS, salvage immunosuppressive regimens have included methotrexate, ATG, or OKT3. The macrolide antibiotic azithromycin has shown efficacy in improving FEV_1.

Rationale for therapeutic apheresis

Initially, ECP was used in the context of refractory BOS (Stages II–III) in which beneficial effect was demonstrated by initial stabilization or improvement in FEV_1. More recent literature suggests that ECP may be an effective therapeutic modality for stabilization of lung function in patients with persistent acute rejection and early BOS (Stages 0-p-1) as well, thus potentially preventing further loss of pulmonary function. The mechanism of action of ECP in this setting remains unclear. Both anti-HLA and "lung-associated self-antigens" (SAgs, tubulin, and collagen) have been proposed to have a role in mediating AMR in the lung allograft ("pulmonary capillaritis"). In a recent study (Baskaran, 2014) use of ECP in lung transplant patients was associated with a reduction in the levels of circulating DSA, Sags, and proinflammatory cytokines. In 2012, the US Centers for Medicare and Medicaid services determined that coverage for ECP in BOS post-lung transplant will be allowed only within the context of a study which involves evidence development. For the treatment of pulmonary AMR (with "pulmonary capillaritis"), few studies have reported the use of TPE (typically in combination with IVIG, and anti-B cell/plasma cell therapies) with variable results. In the area of desensitization of highly alloimmunized lung transplant waitlisted patients, use of a multimodal desensitization protocol including TPE, rituximab, bortezomib, and steroids in cohort of patients (n = 8) did not appear to significantly reduce pretransplant HLA antibodies (Snyder, 2014) and survival among the treated group was comparable to untreated cohort.

Technical notes

One cycle consists of ECP on two consecutive days. In a large case series of ECP in BOS: a total of 12 cycles over 6 months were administered: 5 during first month, biweekly for 2 months (four cycles), and then monthly for 3 months (three cycles).

Volume treated: Typically, MNCs are obtained from processing 1.5 L of whole blood, but the volume processed may vary based on patient weight and HCT. The 2-process method collects and treats MNCs obtained from processing 2 TBV.	**Frequency**: ECP: As above; TPE: Every other day
Replacement fluid: ECP: NA; TPE: Albumin, plasma	

Duration and discontinuation/number of procedures

The optimal duration is unknown. In published studies, the number of treatment cycles for ECP ranged between 6 and 24. If clinical stabilization occurs with ECP, long-term continuation may be warranted to maintain clinical response. For AMR, treatment may be discontinued upon reversal of rejection or treatment futility.

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MALARIA

Incidence: 214 million cases worldwide in 2015; 1,500 cases in US	Indication Severe	Procedure RBC exchange	Recommendation Grade 2B	Category III
No. of reported patients: < 100 RBC exchange; >300 Manual ET	RCT	CT	CS	CR
RBC exchange	0	1(415)[a]	9(37)	14(18)
Manual ET	0	8(279)	8(101)	13(13)

[a]Automated and manual RBC exchange. ET = exchange transfusion.

Description of the disease

Malaria is vector-borne protozoal infection caused by *Plasmodium vivax, P. ovale, P. malariae*, or *P. falciparum*. Although mortality has declined worldwide, malaria still causes 500,000 dealths annually. The highest mortality occurs with *P. falciparum* in Africa in pregnant women, nonimmune travelers, those with HIV/AIDS, and children <5 years. The intraerythrocytic stage of *Plasmodia* life cycle is responsible for the pathological disease manifestations. Parasitemia leads to RBC rigidity and aggregation, microvascular obstruction, hemolysis, and activation of inflammatory cells and cytokines. *P. falciparum* is responsible for most severe malaria cases, characterized by high-grade (> 5%) parasitemia with or without single organ or multisystem dysfunction (impaired consciousness, seizures, pulmonary edema, acute respiratory distress syndrome, shock, disseminated intravascular coagulation, acute kidney injury, hemoglobinuria, jaundice, severe anemia (Hgb < 5 g/dL), acidosis, and hypoglycemia). Mortality rate with severe *falciparum* malaria is 5–20%. Poor prognostic features include older age, shock, acute kidney injury, acidosis, decreased level of 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.

Current management/treatment

Malaria treatment is based on clinical status of the patient, *Plasmodium* species involved, and drug-resistance pattern predicted by geographic region of acquisition. Management of imported, uncomplicated malaria in the US is outlined in guideline documents available from the Centers for Disease Control and Prevention (CDC). Severe malaria should be treated promptly with intravenous quinidine gluconate and 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. *P. falciparum* with severe anemia, hypoxemia, hyperparasitemia, neurologic manifestations, or metabolic derangements, particularly in children, asplenic, or immunocompromised individuals, requires aggressive parenteral antimalarials. Intensive care support is also often necessary.

Rationale for therapeutic apheresis

RBC exchange or manual exchange transfusion (ET; with whole blood or RBC replacement) in severely ill patients with hyperparasitemia (> 10%) appears to improve blood rheological properties, capillary perfusion, and microcirculatory flow by removing infected RBC thus reducing parasite load and modulating cytoadherence. Whole blood ET may also reduce pathogenic humoral mediators, such as parasite and host toxins, hemolytic metabolites, cytokines, and replenish deficient proteins (ADAMTS13, clotting factors). CRs have described rapid clinical improvement and improved parasite clearance times with severe *P. falciparum* when RBC exchange or manual ET is used in conjunction with intravenous quinidine therapy. However, parasite clearance time with artesunate alone is rapid and similar to that achieved by automated RBC exchange. The role for and potential benefit of automated or manual ET in severe malaria is controversial and based on observational retrospective clinical data. Meta-analysis of 279 patients from eight case-controlled trials found no survival benefit of manual ET compared to antimalarials and aggressive supportive care. Notably, there were major differences in ET methodologies, severity of illness in transfusion versus non-transfusion groups and other confounding variables that question accuracy of these comparisons and the analyses. The CDC reported on 101 patients with severe malaria who received ET compared to 314 who did not and demonstrated no difference in mortality and thus no longer recommend ET use. Limitations to this underpowered study were lack of critical data on ET specifics (manual versus automatic, full or partial; whole blood versus RBC), lack of parasitemia level in many patients, lack of survival data in ET patients, exclusion of ET survival cases, and imperfect matching of cases and controls. Fatal cases that received ET often received this therapy late in their disease course (CDC MMR reports). Moreover, sicker patients received ET in the studies hampering the ability to accurately interpret mortality data. The 2007 UK treatment guidelines for severe malaria suggest consideration of RBC exchange for severely ill patients with > 10% parasitemia. WHO guidelines make no recommendation regarding ET use, citing lack of consensus on indications, benefits, dangers, and practical technical details. Rare CRs have described using adjunctive TPE with automated RBC exchange; however, lack of published experience precludes assessment of this in patients with severe malaria. Thus, until more effective adjunct therapy is developed, patients with poor prognostic markers may be considered for adjunct RBC exchange.

Technical notes

Automated apheresis instruments calculate the amount of RBCs required to achieve the desired post-procedure hematocrit, fraction of RBCs remaining and, by inference, the estimated final parasite load. One 2 volume RBC exchange can reduce the fraction of remaining patient RBCs to roughly 10–15% of the original. The additional risks in developing countries may include transfusion transmitted infections.

Volume treated: 1–2 total RBC volumes	Frequency: 1–2 treatments
Replacement fluid: RBCs (consider leukoreduced)	

Duration and discontinuation/number of procedure

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

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RBC exchange

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MULTIPLE SCLEROSIS

Incidence: 5–30/100,000/year (US)	Indication	Procedure	Recommendation	Category
	Acute CNS inflammatory demyelinating	TPE	Grade 1B	II
	Acute CNS inflammatory demyelinating	IA	Grade 2C	III
	Chronic progressive	TPE	Grade 2B	III

No. of reported patients: > 300	RCT	CT	CS	CR
Acute CNS inflammatory demyelinating	3(306)	1(41)	10(169)	NA
Chronic progressive	7(285)	0	10(165)	NA

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. Four immunopathological patterns of demyelination have been described 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 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's syndrome; see NMO spectrum disorders fact sheet).

Current management/treatment

The pathophysiology of MS remains incompletely understood but autoimmunity, involving both the humoral and cellular components of the immune system, along with genetic and environmental factors play a role. Current disease modifying therapies used in MS include: interferon beta, glatiramer acetate, azathioprine, mitoxantrone, cyclophosphamide, intravenous immunoglobulin, rituximab, natalizumab, fingolimod, and others depending on the disease severity and treatment response. 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.

Rationale for therapeutic apheresis

TPE may benefit MS patients by removing autoantibodies and/or immune complexes or modulating immune response. In acute, severe attacks of MS in patients who fail initial treatment with high-dose steroids, TPE may be beneficial (Gwathmey, 2014). 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, 2005). Clinical improvement may not necessarily be accompanied by resolution of active lesions on imaging (Meca-Lallana, 2013). Use of IA in this setting has also been reported in multiple case series which suggest a similar efficacy compared to TPE (Koziolek, 2013). A recent case series retrospectively evaluated 60 patients and observed an 88% response rate (Heigl, 2013). Several controlled clinical trials demonstrate minimal to no benefit of TPE in chronic progressive MS (Klingel, 2013). A few retrospective studies of patients with RRMS have demonstrated improvement with ECP and this has been proposed as an area for further research.

TPE has also been used for drug removal in MS patients treated with natalizumab who developed progressive multifocal leukoencephalopathy (see Progressive multifocal leukoencephalopathyassociated with natalizumab fact sheet).

Technical notes

All but one study to date on the use of IA in MS have used single-use tryptophan adsorbers.

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 ∼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.

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MYASTHENIA GRAVIS

Incidence: 1/100,000	Indication	Procedure	Recommendation	Category
	Moderate–severe	TPE	Grade 1B	I
	Pre-thymectomy	TPE	Grade 1C	I
No. of reported patients: > 300	RCT	CT	CS	CR
Moderate–severe	8(279)	8(2837)	30(556)[a]	NA
Pre-thymectomy	0	5(342)	2(51)[a]	NA

[a]6 (405) CS contained both groups of patients; CS added anti-MuSK 110, 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, usually improving with rest. Common presentation includes ptosis and diplopia with more severe cases having facial, bulbar, and limb muscle involvement. Most commonly in 20–40 years women, but occurs in other ages including juvenile form, and in neonates in rare cases (due to passive maternal antibody transfer). Most common causative antibody is directed against acetylcholine receptor (anti-AChR) on the post-synaptic surface of the motor end plate. Ordinarily, motor nerves release neurotransmitter acetylcholine (ACh) at neuromuscular junction. ACh crosses synaptic space to muscle surface binding to AChR and stimulates an action potential and muscle contraction. Anti-AChR reduces the number of available AChR, decreasing the action potential achieved. Anti-AChR level does not correlate with disease severity; severe disease can occur without detection of this antibody. Antibodies to muscle specific receptor tyrosine kinase (MuSK) are detected in ∼50% of anti-AChR seronegative disease. MuSK mediates formation of the neuromuscular junction and induction of AChR. Antibody against low-density lipoprotein receptor-related protein 4 (LRP4) has also been described. LRP4 is an agrin receptor, which is essential for agrin-induced activation of MuSK and AChR clustering and neuromuscular junction formation. Other antibodies include anti-titin, and anti-agrin. 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 (hyperplasia or thymoma) are commonly associated with MG.

Current management/treatment

Modern treatment regimens have decreased MG mortality from 30% to < 5%. Four major treatment approaches include cholinesterase inhibitors, thymectomy, immunosuppression, and either TPE or IVIG. Cholinesterase inhibitors (pyridostigmine bromide) delay breakdown and increase availability of ACh at motor end plate and lead to variable strength improvement. Cholinergic side effects, including diarrhea, abdominal cramping, increased salivation, sweating, and bradycardia, are dose limiting and lead to non-compliance. Thymectomy leads to clinical improvement in many patients < 65 years but may take years for benefits. Immunosuppressive drugs (corticosteroids, azathioprine, cyclosporine, tacrolimus) have delayed effect and are important for long-term rather than short-term management. Rituximab demonstrated effectiveness in many cases, particularly in MuSK-MG. Other promising monoclonal antibodies include belimumab, eculizumab.

Rationale for therapeutic apheresis

TPE is used to remove circulating autoantibodies, particularly 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-MG. TPE may be more effective if initiated earlier in the disease's course.

In one RCT 87 patients with major exacerbations underwent three every other day 1.5 TPV 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. Second RCT that included 12 stable patients with moderate–severe disease found TPE to be better at 1 week, equivalent improvement at 4 weeks, and neither to show improvement at 16 weeks. Third RCT included 84 worsening moderate–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% IVIG and 65% TPE, and 18% worsened IVIG and 2% 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.

Additionally, 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 post-procedure prolonged intubation.

DFPP has been shown to be beneficial as well. In addition, newer technology using specific adsorbents for MG autoantibodies is being developed.

Technical notes

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

Duration and discontinuation/number of procedures

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

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MYELOMA CAST NEPHROPATHY

Incidence: 1/100,000/yr		Procedure	Recommendation	Category
		TPE	Grade 2B	II
No. 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 (also known as cast nephropathy) accounts for ~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, and toxic effects of light chains on distal tubular epithelium.

Current management/treatment

Therapeutic approaches include inducing an alkaline diuresis through intravenous administration of normal saline and sodium bicarbonate with or without loop diuretics in order to solublize positively charged light chains. Anti-myeloma chemotherapy consisting of an alkylating agent and a corticosteroid are used to diminish M-protein production. More recently, immune modulation (thalidomide, lenalidomide) and proteasome inhibition (bortezomib) have emerged as highly 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 traditional primary modes of therapy, TPE has been used to acutely decrease the delivery of light chains to the renal glomerulus for filtration, since early reduction in ligh chain levels have been proven to be associated with better renal outcomes and overall survival. Peritoneal dialysis and "high cut off membrane" hemodialysis (but not conventional hemodialysis) can also remove light chains but with lower efficiency than TPE. A randomized trial of 21 patients with biopsy-proven myeloma kidney who received melphalan, prednisone, and forced diuresis with or without TPE showed no statistically significant outcome differences (Johnson, 1990). 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 endorsement of TPE for myeloma kidney by the Scientific Advisors of the International Myeloma Foundation. The largest ($n = 104$) 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/1.73m² at 6 months (Clark, 2005). This study has called into question TPE's role in the treatment of myeloma kidney in an era of rapidly effective chemotherapy. However, this study has been criticized in that most of the enrolled patients were not proven to have cast nephropathy by renal biopsy, and 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. In all cases ultimate survival depends on a satisfactory response to chemotherapy.

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.

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 addition of TPE. For patients who are oliguric, who excrete ≥ 10 g of light chains per 24 h, or whose serum creatinine is ≥ 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.

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NEPHROGENIC SYSTEMIC FIBROSIS

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

No. of reported patients:<100	RCT	CT	CS	CR
ECP	0	0	5(17)	2(3)
TPE	0	0	5(11)	2(3)

Description of the disease

Nephrogenic systemic fibrosis (NSF), formerly called nephrogenic fibrosing dermopathy, is a rare but severe systemic disorder in patients with acute or chronic kidney disease (CKD), almost exclusively associated with the administration of gadolinium (Gd) containing contrast agents. Occuring in 0–18% of patients with kidney disease (low GFR) who received Gd. Newer cases have been reported and the highest risk group are patients with GFR <15 mL/min who receive Gd. A large number of cases with CKD have been in patients with Stage IV (GFR 10–29 mL/min/1.73 m^2) or Stage V (dialysis dependent) CKD. It has not occured in those with a GFR >60 mL/min/1.73 m^2. The mean time interval between Gd administration and NSF onset is 2 days (same day to 18 months). Higher dose of Gd has higher risk than standard dose. NSF occurs also in patients with hepatorenal syndrome and in perioperative period following liver transplantation. Additional factors associated 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 include hair loss, gastroenteritis, conjunctivitis, bilateral pulmonary infiltrates, and fever. Over 6–12 months, swelling, pruritus, and sensory changes resolve while skin progresses to 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, disease progresses to death within weeks to months while the remaining demonstrate slow progression. Cure is rarely reported. Overall mortality rate is up to 30%.

The pathophysiology is uncertain. Advanced kidney disease markedly prolongs Gd contrast excretion. 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 autopsies.

Current management/treatment

Replacement of renal function through renal transplant has been associated with cessation of progression and reversal in some patients. It should be noted that dialysis has not been associated with improvement once symptoms are established. Initiation of prophylactic hemodialysis shortly after exposure to Gd may decrease the likelihood of the harmful effect. Additional therapies include steroids, immunosuppression, imatinib messylate, chelation therapy with sodium thiosulfate, TPE, and ECP. Avoidance of Gd administration, if possible, has been recommended for patients with GFR <30 mL/min; resulting 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. Patients demonstrated improvement including skin softening (9/14), increased range of motion (ROM) (4/14), improved ambulation (1/14), and improvement from wheel chair bound to walking (1/14). Additional reported changes include decreased swelling, pain, and paresthesias. 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. Improvement includes skin softening (16/20), increased ROM (12/20), improved ambulation (4/20), and improvement from being wheel chair bound to walking (3/20). Additional reported changes include 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: Typically, MNCs are obtained from processing 1.5 L of whole blood, but volume processed varies based on patient weight and HCT. 2-process method collects and treats MNCs obtained from processing 2 TBV; TPE: 1–1.5 TPV
Replacement fluid: ECP: NA; TPE: albumin

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

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 treatment initiation. Time to response with ECP ranged from 4 to 16 months.

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References

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NEUROMYELITIS OPTICA SPECTRUM DISORDERS

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

No. of reported patients: 100–300	RCT	CT	CS	CR
Acute	0	2(59)	12(104)	31(41)
Maintenance	0	0	1(7)	1(2)

Description of the disease

Neuromyelitis optica spectrum disorders (NMOSD), previously neuromyelitis optica (NMO) and Devic's disease, is an inflammatory demyelinating disorder characterized by attacks within 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 visual phenomena. Symptoms of hypothalamic and brainstem involvement, occuring in 15% of patients, include hiccups, intractable nausea, and respiratory failure. NMOSD differs from multiple sclerosis (MS) as it is more typical in non-whites (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≤ vertebral segments), absence of CSF oligoclonal IgG bands but presence of CSF leukocytosis, and brain MRI is atypical for MS. NMOSD is associated with other autoimmune diseases, such as systemic lupus erythematosus (SLE), Sjögren's, and myasthenia gravis, and viral infections and vaccinations. NMOSD 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 90% 5-year survival rate. Approximately 80% of patients with NMOSD have relapsing course, which has a poor prognosis: 50% of patients become legally blind or wheelchair bound and 30% die of respiratory failure within 5 years. The disease worsens by incomplete recovery with each acute attack.

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

Current diagnostic criteria are: optic neuritis, acute myelitis, and at least two of three supportive criteria: contiguous spinal cord MRI lesions extending over ≥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 daily × 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, cyclophosphamide, prednisone, IVIG, and mycophenolate mofetil. Newer agents such as IL-6 inhibitors (tocilizumab) and complement inhibitors (eculizumab) show promising results in early clinical trials.

Risk factors for recurrence include Sjögren's syndrome seropositivity (SSA-Ab), 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 pathogenesis of NMOSD, it is reasonable to postulate that TPE has a role in the treatment. A number of case reports have shown TPE benefits in corticosteroid-refractory NMOSD exacerbation. One non-randomized control study showed TPE added to pulsed intravenous corticosteroids is more effective than pulsed intravenous corticosteroids alone in patients with acute optic neuritis and limited forms of NMOSD. 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 NMOSD relapse. One study showed that patients who had preserved reflexes and received TPE early after attack (<20 days) had a high likelihood of responding to TPE, but the optimal time to start TPE needs to be determined. In a 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 received steroids.

DFPP has also been reported to be used successfully to control NMOSD exacerbation.

Technical notes

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

Duration and discontinuation/number of procedures

The majority of studies performed five procedures on average for acute exacerbation, but ranged from 2 to 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 3–5 weeks) showed varying degrees of improvement and reduction in the number of NMOSD exacerbation.

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N-METHYL-D-ASPARTATE RECEPTOR ANTIBODY ENCEPHALITIS

Incidence: Rare		Procedure TPE	Recommendation Grade 1C	Category I
No. of reported patients: 100–300	**RCT** 0	**CT** 0	**CS** 5(221)	**CR** 39(41)

Description of the disease

Anti-*N*-methyl D-aspartate receptor (NMDAR) encephalitis is an acute autoimmune neurological disorder first described by Dalmau (2007). It is characterized by IgG antibodies targeting the synaptic GluN1 (also known as NR1) subunit of the NMDAR. Approximately 70% of patients present with a flu-like prodrome (lasting ~5 days to 2 weeks) that progress to psychiatric manifestations and movement disorders (dyskinesia), seizures, and cognitive decline. As symptoms progress there is decreased consciousness, periods of agitation alternating with catatonia, autonomic dysregulation such as poor control of blood pressure, arrhythmias, respiratory disturbances, and hypo- or hyperthermia. If the impairment of autonomic functions progresses, the disease can be fatal, especially if patients are not adequately treated or are unresponsive to treatment. The disease usually occurs in young adults and children, predominantly females, although it can affect patients of all ages. Approximately 50% of women have an underlying neoplasm; usually ovarian teratoma. Definitive diagnosis can be made by the detection of NMDAR autoantibodies in the serum, and more specifically in the CSF. Imaging, EEG, and brain biopsy are typically nondiagnostic. Delay in diagnosis is common as anti-NMDAR encephalitis is often mistaken for psychosis or viral encephalitis. The California Encephalitis Project found that anti-NMDAR encephalitis was a more prevalent etiology of encephalitis than any individual virus in children (Gable, 2011). Similarly, in a population-based study in England, anti-NMDAR encephalitis was the second most common autoimmune encephalitis after acute demyelinating encephalomyelitis.

Current management/treatment

Once diagnosed immunotherapy should be initiated, and a search for potential underlying tumor performed. In cases with associated tumor, optimal response to immunotherapy is contingent upon tumor removal, resulting in better outcomes and fewer neurological relapses. First-line immunotherapies include intravenous high-dose steroids (methylprednisolone), IVIG, and/or TPE. Approximately 50% of patients respond to these first-line immunotherapies; the other 50% require second-line therapies, such as rituximab or combination of rituximab and cyclophosphamide. Approximately 75–80% of patients recover or improve (50% within 4 weeks of treatment), but in 20% there are substantial deficits or death. Recovery is gradual and symptoms begin disappearing in reverse order of appearance. In the largest cohort study of 577 patients (Titulaer, 2013), predictors of good outcome were early treatment and no admission to intensive care unit. Relapses occur in 12–20% of cases often presenting as fragments of the syndrome (perhaps due to prompt diagnosis). Patients who receive second-line immunotherapies have fewer relapses, thus, leading some to use rituximab initially. Patients who do not respond to treatment, or who have relapses, should be reassessed for the presence of an underlying contralateral or recurrent teratoma. Disease activity appears to correlate with antibody levels e.g. decline/undetectable during remission, and increase with relapse thus, making quantitation of autoantibodies helpful for patient management and monitoring response to immunotherapy. High initial titers are associated with teratoma, poorer neurological outcome, and longer time for response to therapy. Psychopharmacological approaches are also used in the treatment of anti-NMDAR encephalitis patients for the management of psychiatric symptoms.

Rationale for therapeutic apheresis

TPE removes the offending antibody, in adjunct to immunotherapy for suppressing antibody production, and teratoma excision, if present, for removing the possible antibody stimulus. Dalmau (2011) proposed a treatment plan consisting of teratoma removal (if present), corticosteroids and/or IVIG and/or TPE (alone or any combination) as the first-line of treatment), and rituximab and cyclophosphamide as the second-line of treatment for non-responders. The exact order of the treatments (corticosteroids, IVIG, and TPE) was not defined. Furthermore, systematic comparisons between the three first-line modalities are unavailable (Titulaer, 2013). Recent case series (Pham, 2011; DeSena, 2015) suggest early initiation of TPE or TPE followed by IVIG provide better outcomes. Furthermore, fewer patients showed improvement following steroids as compared to immediately following TPE. It was also noted that the point of largest sustained improvement is when TPE should have achieved reasonable efficacy, between the third and fifth exchanges (DeSena, 2015). Other case reports or case series regarding the use of TPE in treating anti-NMDAR encephalitis describe conflicting results. In a recent European series (Kohler, 2015), IA was tried in nine patients in conjunction with steroids or IVIG. A median of six IA treatments were given with clinical improvement in most patients.

Technical notes

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

Duration and discontinuation/number of procedures

IgG antibody needs to equilibrate between the intravascular and extravascular spaces. Moreover, in anti-NMDAR encephalitis, the antibody also needs to equilibrate between the plasma and CSF. Therefore, optimized therapy would include 5–6 TPE procedures on alternate days. Recovery has been reported to be a gradual process with patients often requiring long period of hospitalization. Hence, it is not surprising that patients reported in the literature did not always improve rapidly after the completion of a course of TPE.

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OVERDOSE, ENVENOMATION, AND POISONING

Incidence: Rare	Indication	Procedure	Recommendation	Category
	Mushroom poisoning	TPE	Grade 2C	II
	Envenomation	TPE	Grade 2C	III
	Drug overdose/poisoning	TPE	Grade 2C	III
No. of reported patients: > 300	RCT	CT	CS	CR
Mushroom poisoning	0	0	11(305)	4(4)
Envenomation	0	0	3(77)	4(4)
Drug overdose/poisoning	0	0	12(215)	>50

Description of the disease

Drug overdose (accidental, intentional, or iatrogenic), envenomation, or poisoning result from exposure to agents or toxins capable of producing tissue injury and/or organ dysfunction. Ingestion, inhalation, and injection are common routes of exposure for drugs and poisons. Envenomation occurs from snakes, spiders, scorpions, or venomous stinging insects. 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 poisoning incidents is accidental and occurs at home, most often involving children < 6 years. Fortunately, serious injury is the exception, not 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 or anti-venoms, when available, are promptly administered. Induced emesis, gastric lavage, and oral administration of activated charcoal may be used to minimize gastrointestinal absorption of ingested substances. Whole-bowel irrigation, another technique available for gastro-intestinal decontamination, is particularly useful for removing poorly absorbed agents that are not adsorbed to charcoal. Forced acid or alkaline diuresis is used to promote the renal elimination of ionized agents that are not strongly bound to proteins. 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.

Rationale for therapeutic apheresis

Amanita mushroom poisoning is the most frequent clinical diagnosis where TPE has been utilized, in addition to other therapies to remove toxin including activated charcoal and forced diuresis. Large case series showed decreased mortality among patients, mostly children, treated with TPE when compared with historical controls. Very early initiation of the treatment (within the first 24–48 h) is recommended. Other environmental exposures where the use of TPE has been described include castor bean ingestion and pesticide/organophosphate poisoning.

TPE has also been used for toxin removal following envenomation from snake or brown recluse spider bites and scorpion or Africanized bee stings. A recently published case series described 37 patients treated with TPE following snake bite when limb swelling did not improve following anti-venom administration and supportive care. All patients survived to discharge with limb preservation (Zengin, 2013).

Reports of the successful use of apheresis in the treatment of various drug overdoses and poisonings are based only on case reports and series (Schutt, 2012). TPE may be used for the removal of drugs with a low volume of distribution (<0.2 L/kg) and/or high-plasma protein binding (>80%). Other important factors include the time between dose administration and TPE initiation and the relationship between the amount of drug removed and the biologic effect. The effect of TPE on the removal of various drug classes has been described (Ibrahim, 2013).

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.

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PARANEOPLASTIC NEUROLOGICAL SYNDROMES

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

No. of reported patients: 100–300	RCT	CT	CS	CR
TPE	0	1(20)	11(100)	19(20)
IA	0	0	1(13)	0

Description of the disease

The paraneoplastic neurologic syndromes (PNS) are a varied group of cancer-related neurologic disorders that are associated with onconeural antibodies (ON-Abs). Those antibodies target antigens that are expressed by both the tumor and the nervous system and mainly recognize intracellular antigens, e.g. Hu, CV2/collapsing response mediator protein 5 (CRMP5), Yo, Tr, and amphiphysin. Since the On-Abs are directed against intracellular antigens, which are not directly accessible to the antibodies, it is presumed that the main pathogenic effect is most probably carried out by cytotoxic T cells mediated immune reaction, resulting in neuronal cell death. A large number of additional antibodies against cell surface or synaptic proteins (e.g., NMDAR, VGKC) associated with paraneoplastic syndromes of the central and peripheral nervous systems and the neuromuscular junction have been described and are reviewed under specific separate fact sheets. PNS is rare, occurring in 0.1–1% of cancer patients. Classical PNS manifestations are subacute cerebellar degeneration which is the most common PNS syndrome, limbic encephalitis (LE), paraneoplastic encephalomyelitis (PEM), Opsoclonus–myoclonus syndrome (OMS), which is the most common pediatric PNS, subacute sensory neuropathy (SSN), chronic gastrointestinal pseudo-obstruction, Lambert–Eaton myasthenic syndrome (LEMS), and dermatomyositis.

The tumors most commonly associated with PNS are those that express neuroendocrine proteins, such as small cell lung cancer (SCLC); tumors that contain nervous tissue, such as teratomas; and tumors that affect organs with immunoregulatory functions, such as thymoma. PNS mostly precede detection of the underlying cancer; patients in whom PNS is strongly suspected but no cancer is identified should undergo periodic cancer screening for at least 5 years.

The diagnostic work-up of a suspected PNS includes proving its immune-mediated nature and ruling out meningeal disease, metastasis, and toxic or metabolic causes. If clinical suspicion of PNS remains high, screening for relevant ON-Abs should be initiated. Their presence or absence helps to further predict the probability and location of underlying cancer. Finally, a tumor screening guided by the clinical information and antibody status should be performed as the frequency, age dependency, and most probable tumor localization are suggested by the clinical syndrome and/or detected antibody.

Detecting ON-Abs, together with a compatible neurological syndrome, has a high specificity for PNS. However, even in patients with definite PNS in a large European network study, only 80% harbored ON-Abs. A recent review reported that 60% of PNS of the central nervous system and less than 20% of those affecting the peripheral nervous system are associated with these antibodies.

Current management/treatment

Treatment of PNS includes antitumor and immunosuppressive therapy. Prompt initiation of anti-tumor therapy upon diagnosis can stabilize symptoms. If symptoms do not stabilize or if no tumor is detected, immunosuppression (usually steroids, TPE, IVIG, or IA) is tried. Aggressive immunosuppression early in the course is recommended in patients who are identified prior to a tumor diagnosis. 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.

Rationale for therapeutic apheresis

The association of syndromes with specific CSF and serum antibodies led to the use of immunosuppressive therapy, including TPE and IA. Most patients treated with TPE have also received immunosuppressive drugs as well as anti-cancer therapy. 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 subacute cerebellar degeneration with anti-Tr antibodies may be more likely to respond to TPE, though many of them do not have malignancy. TPE has not been shown to be effective in syndromes with ON-Abs, e.g. Hu, Yo as it does not target the cell-mediated autoimmunity directly. A series of 13 patients with OMS or subacute cerebellar degeneration were treated with staphylococcal protein A IA. There were three complete and three partial neurological remissions; all subsequently relapsed. Although the exact mechanism of action of protein A IA is not well understood, data suggest that it results in a reduction of circulating IgG antibodies and immune complexes and an increase in natural killer cell activity.

Technical notes

Volume treated: TPE: 1–1.5 TPV; IA: 2–4 TPV
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. In one reported clinical trial patients were treated with Protein A IA twice weekly for 3 weeks.

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PARAPROTEINEMIC DEMYELINATING NEUROPATHIES/CHRONIC ACQUIRED DEMYELINATING POLYNEUROPATHIES

Incidence: Anti-MAG neuropathy: rare; MMN: Rare; MGUS: < 3% of population > 50 yr; Multiple myeloma: 4–6/100,000/yr	Indication	Procedure	Recommendation	Category
	Anti-MAG neuropathy	TPE	Grade 1C	III
	MMN	TPE	Grade 1C	IV
	IgG/IgA	TPE	Grade 1B	I
	IgM	TPE	Grade 1C	I
	Multiple myeloma	TPE	Grade 2C	III
	IgG/IgA/IgM	IA	Grade 2C	III

No. of reported patients: 100–300		RCT	CT	CS	CR
IgG/IgA	TPE	1(39)[a]	0	3(29)	N/A
IgM	TPE	1(39)[a]	0	6(102)	N/A
Multiple myeloma	TPE	0	0	1(4)	1(1)
IgG/IgA/IgM	IA	0	0	1(3)	4(5)
MMN	TPE	0	0	1(7)	8(10)
Anti-MAG[b] neuropathy	TPE	0	0	1(19)	NA

[a]Same trial. [b]Not inclusive, due to change of disease definition in later studies. MMN = multifocal motor neuropathy.

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 balls of the feet or tips of toes, usually symmetric and graded distally. Nerve fibers are affected according to axon length, without regard to root or nerve trunk distribution (stocking-glove distribution). Polyneuropathies are diverse in time of onset, severity, mix of sensory and motor features, and presence or absence of positive symptoms. IgA and IgG monoclonal gammopathy can be associated with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), POEMS syndrome, and other neuropathic syndromes associated with monoclonal gammopathy.

Chronic acquired demyelinating polyneuropathies (CADP), newer disease classification, include a variety of neuromuscular disorders resulting from immune-mediated demyelination: CIDP, multifocal motor neuropathy (MMN), multifocal acquired sensory and motor neuropathy (MADSAM), neuropathy associated with monoclonal IgM antibodies to myelin-associated glycoprotein (MAG; anti-MAG neuropathy), POEMS syndrome, and other neuropathic syndromes associated with monoclonal gammopathy. The classification of CADP takes into consideration both disease presentation and pathological etiology, thus better defines effective treatment. The diagnosis algorithm is first based on the presence of either motor or sensorimotor neuropathy. For patients with motor neuropathy, combination of conduction block and demyelination would lead to the diagnosis of MMN. For patients with sensorimotor neuropathy, after confirmation of demyelination, further classification is based on antibody specificity.

Typical presentation of MMN includes chronic asymmetric distal-limb weakness, atrophy, and fasciculation that affect distal arm more frequently than leg; usually follows peripheral nerve distribution with limited or no sensory symptoms. It occurs male > female, in fifth decade of life. Although resembling MMN, MADSAM is separate disease, a multifocal inflammatory demyelinating polyneuropathy, and is considered by some as a multifocal variant of CIDP. Once MMN is ruled out, the detection of anti-MAG in IgM monoclonal gammopathy associated neuropathy establishes the diagnosis of anti-MAG neuropathy. Typical presentation of anti-MAG neuropathy include distal, predominantly sensory large fiber ataxic neuropathy, some patients may also have neurogenic tremor in the arms. In addition to anti-MAG, sulfated glucuronyl paragloboside antibodies may also be detected. Disease progression is variable, some may take years or decades and others may have acute accelerations. Anti-MAG neuropathy is associated with MGUS, but in 12–35% cases associated with Waldenström macroglobulinaemia or B-cell lymphoma.

Current management/treatment

Optimal treatment is unknown. Response to immunopressive drugs varies. Corticosteroids alone tend to be more effective in IgG- and IgA-polyneuropathies with a response rate of 40–60%. For MMN patients, combination of corticosteroids and TPE may result in variable response, from partial and transient response, no response, to possible aggravation of the neuropathy. Cyclophosphamide has been used and can lead to transient improvement, but its use is limited by its toxicity. Several uncontrolled and placebo-controlled studies demonstrate up to 94% patients respond to IVIG. Response to IVIG is typically seen within several days and may last several weeks to months. IVIG has also been used for the prevention of disease progression. IVIG has become the standard of care for MMN.

For anti-MAG neuropathy, steroids have not been shown to be effective, and treatment effect of IVIG or TPE is often transient. Cytotoxic agents can result in some improvement, but use is limited due to toxicity. Use of rituximab can result in marked improvement. In one RCT with 26 patients, patients who received rituximab had significant improvement in the "time to walk 10 m" than that in placebo group. Similar results were found in another trial with 54 patients. Clinical improvement is often seen when there is at least a 50% reduction of serum IgM.

Rationale for therapeutic apheresis

The rationale for using TPE is to remove anti-MAG or other antibodies. It is suggested (Cortese, 2011) that TPE is probably more effective for IgA and IgG MGUS-associated polyneuropathy, and not for IgM-MGUS. For MMN, the result has been ranged from partial and transient response, no response, to possible aggravation of the neuropathy. In one report of seven patients (Lehmann, 1998), only two had some improvement in function and two had slight deterioration of function, whereas all patients had worsened electrophysiological parameters post TPE. For anti-MAG neuropathy, TPE may have a transient response. In one report, out of 19 patients (Gorson, 2001) who had anti-MAG neuropathy (although some of them had abnormal conduction velocities) and received TPE, 40% had a transient effect, but most of them had a relapse upon stopping of TPE.

Currently more effective treatments are available for MMN and anti-MAG neuropathy, TPE is rarely indicated for these conditions.

Technical notes

Volume treated: 1–1.5 TPV	Frequency: See below
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

Typical course is 5–6 treatments over 10–14 days.

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

Incidence: PANDAS: unknown;SC: 10–50% of ARF patients	Indication	Procedure	Recommendation	Category
	PANDAS, exacerbation	TPE	Grade 1B	II
	SC, severe	TPE	Grade 2B	III

No. of reported patients: < 100	RCT	CT	CS	CR
PANDAS	1(29)	0	1(35)	4(4)
SC	1(18)	0	0	0

PANDAS = Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; SC = Sydenham's chorea; ARF = acute rheumatic fever

Description of the disease

PANDAS and SC are both pediatric post-infectious autoimmune neuropsychiatric disorders which typically follow Group-A beta-hemolytic streptococcus (GABHS) infection. Both may have a shared etiopathogenesic basis. Antibodies produced against GABHS, especially streptococcal M-proteins, cross-react with neurons of the basal ganglia and are thought to play a role in the pathogenesis of this family of disorders. GABHS infection has been associated with childhood-onset neuropsychiatric disorders in susceptible individuals. A subgroup of these disorders is identified by the acronym PANDAS, which was first described in 50 children by Swedo (1998). The five diagnostic criteria proposed for PANDAS include: (1) presence of obsessive compulsive disorder (OCD) and/or a tic disorder, (2) prepubertal onset, (3) abrupt onset or exacerbation of symptoms with an episodic (relapsing-remitting) course, (4) temporal association of symptoms with GABHS infection, and (5) association with neurological abnormalities including choreiform movements. A diagnosis of PANDAS may only be made after SC and acute rheumatic fever (ARF) have been excluded as a cause of a child's symptoms. The onset of PANDAS is acute and abrupt, often associated with co-morbid neuropsychiatric symptoms, including mood lability, attention deficit-hyperactivity 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 ARF, occurs in an estimated 10–50% of patients with ARF, typically resolving after 3–18 months. The major clinical manifestations include chorea, hypotonia, and emotional lability. SC is self-limiting and resolves after 6–9 months, but recurrence may be more common than previously appreciated (up to 40%). The peak age of onset for PANDAS and SC are 6–7 years and 8–9 years, respectively, with male predominance in PANDAS (3:1) and female predominance in SC (2:1). No laboratory tests are specific for the 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., Antistreptolysin O (ASO)] supports the diagnosis of both. Elevated levels of antineuronal antibodies and/or anti-basal ganglia antibodies have been reported in both entities. MRI studies have demonstrated striatal enlargement in basal ganglia.

Current management/treatment

Initial treatments for PANDAS include cognitive behavioral therapy and/or anti-obsessional 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 children with PANDAS. 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/day 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. A randomized placebo-controlled trial of IVIG compared to 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. This effect appeared to be sustained on 1-year follow-up. The TPE group appeared to have greater tic symptom relief than did the IVIG group. In a recent large retrospective series of TPE in 35 patients with PANDAS (Latimer, 2015), patients showed significant improvement in symptoms after both short- and long-term follow-up. In this study, surprisingly, the duration of illness preceding TPE was not correlated with degree of improvement. A randomized controlled study on 18 patients with SC showed that the mean chorea severity scores decreased by 72%, 50%, and 29% in the IVIG, TPE, and steroid groups, respectively, suggesting IVIG/TPE-mediated benefit, however these differences did not reach statistical significance.

Technical notes

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

Duration and discontinuation/number of procedures

Three to six procedures are performed over 1–2 weeks. There is limited data on benefit of repeat TPE treatment courses.

References

As of August 12, 2015, 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.

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PEMPHIGUS VULGARIS

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

No. 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	1(6)	6(35)	5(5)

Description of the disease

Pemphigus vulgaris is a rare, potentially fatal, autoimmune mucocutaneous blistering disease. Genders are equally affected with typical age of onset 60–80 years. Patients present with skin lesions, recurrent and relapsing flaccid blisters, which are located on epidermal or mucosal surface. The lesions peel superficially or detach easily. A large surface of skin can be affected leading to situations akin to severe burn. Pathology of pemphigus vulgaris is characterized by the in vivo deposition of autoantibody, directed against Dsg 1 and 3 (desmoglein 1 and 3), on the keratinocyte cell surface. 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. Dsg1 and 3 autoreactive CD4+ T-cells are detected in patients.

Current management/treatment

Treatment, 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 30%. However, long-term administration of high dose corticosteroids can be associated with severe adverse effects. Other therapeutic options include dapsone, gold, and systemic antibiotics, which are often used in combination with other immunosuppressant agents (azathioprine, methotrexate, cyclophosphamide). Other therapies, some experimental, used include mycophenolate mofetil, chlorambucil, cyclophosphamide, TPE, ECP, IVIG, rituximab, cholinergic receptor agonists, desmoglein 3 peptides and p38 mitogen-activated protein kinase inhibitor.

Rationale for therapeutic apheresis

The rationale for using TPE and IA in pemphigus vulgaris treatment is because there is 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). The duration of disease prior to TPE use ranged 1 month to 25 years. The TPE goal was to reduce the level of autoantibodies and improve clinical symptoms. In one multicenter RCT patients were randomized into prednisolone alone ($n = 18$) and prednisolone plus 10 large volume TPE ($n = 22$) over four weeks (Guillaume, 1988). There were four septic deaths and no steroid sparring effect in TPE arm. IA has been promoted in Europe with increasing number of patients treated and reported clinical responses. Monocentric CRs and CSs showed in the adjuvant setting decrease of the circulating antibodies, which correlated to the improvement of bullous-erosive lesions, and corticoid sparing effect.

Technical notes

TPE protocols vary widely in volume treated (400–4000 mL, treatment frequency) and have been based on observed clinical response after each treatment. Though, more recent reports noted that 1 TPV is preferable in patients who are resistant to conventional therapy. Autoantibody levels rebounded within 1–2 weeks after TPE discontinuation, thus corticoids were used for continued immunosuppressive therapy. Clinical response with ECP was observed after 2–7 cycles (two daily procedures per month). Total number of cycles varied 2–51. In one report 100% clinical response with decreased autoantibody titer was reported, follow-up 4–51 months. The disease was controlled in most patients; seriods could be tapered but rarely able to be discontinued.

Volume treated: TPE: 1–1.5 TPV; ECP: Typically, MNCs are obtained from processing 1.5 L of whole blood, but volume processed varies based on patient weight and HCT. 2-process method collects and treats MNCs obtained from processing 2 TBV; IA: 2–4 TBV
Replacement fluid: TPE: Albumin, plasma; ECP: NA; IA: NA

Frequency: TPE: Daily or every other day; IA: First week 3 daily, than weekly and tapering; ECP: Two consecutive days (one series) every 2 or 4 weeks

Duration and discontinuation/number of procedures

Approach should include monitoring of autoantibody titers and clinical symptoms. For TPE and IA, lack of clinical response after a trial period with concomitant adequate immunosuppression should be sufficient to discontinue treatment. For ECP, treatments were continued until clinical response was noted.

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PERIPHERAL VASCULAR DISEASES

Incidence: 3–10% of population (US)		Procedure LDL apheresis	Recommendation Grade 1B	Category II
No. of reported patients: 100–300	RCT 1(42)	CT 0	CS 6(126)	CR 2(2)

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 (or arms). 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 is more common in men > 50 years. Risk factors include smoking, diabetes mellitus, dyslipidemia, hypertension, coronary artery disease, renal disease on hemodialysis, and cerebrovascular disease. PVD is a strong risk factor for cardiovascular disease. Pathophysiological factors involving PVD include atherosclerosis, endothelial cell dysfunction, and defective nitric oxide metabolite physiology.

Clinical presentation of PVD 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, 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 PVD 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.

PVD is commonly categorized with the Fontaine stages: Stage I: mild pain when walking (claudication), incomplete blood vessel obstruction; Stage II: 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 III: pain while resting (rest pain), mostly in the feet, increasing when the limb is raised; and Stage IV: biological tissue loss (gangrene) and difficulty walking.

Current management/treatment

Management of PVD includes risk reduction, such as smoking cessation, optimal 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 to be used in Fontaine's Stage II 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. LDL apheresis has been shown to enhance peripheral microcirculation, probably by increasing the production of nitric oxide and bradykinin, reducing blood viscosity and adhesion molecules.

One RCT in men with primary hypercholesterolemia and extensive coronary atherosclerosis, randomized patients to receive either biweekly LDL apheresis plus simvastatin ($n = 21$) or simvastatin ($n = 21$) only (Kroon, 1996). LDL apheresis plus simvastatin arm showed decrease in levels of apolipoprotein B, total cholesterol, and lipoprotein(a) levels, decreased intima-media thickness of the carotid artery and prevented increase in the number of clinically significant stenosis in the lower limbs as compared to the control arm. Kobayashi (2005) studied 28 patients with PVD treated with 10 sessions of LDL apheresis (2/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, 2006) demonstrated improvement in physiological parameters such as ABI, maximum tolerated walking distance (MTWD), and clinical symptoms in 31 patients with PVD after an average of 9.6 ± 0.8 sessions of LDL apheresis. Ebihara (2007) also showed a significant enhancement in tissue blood flow of both the head and lower limbs after LDL apheresis treatment in 18 patients. Similarly, clinical improvement was observed in 10 of 19 patients who were hemodialysis patient with PVD and treated with 10 session of LDL apheresis (Tsurumi-Ikeya, 2010). In the patients who responded, LDL apheresis results in short-term decrease in the total cholesterol and LDL cholesterol and long-term reduction of the circulating levels of oxidized LDL, CRP, and fibrinogen.

Technical notes

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: 3,000–5,000 mL of plasma	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.

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As of August 27, 2015 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.

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PHYTANIC ACID STORAGE DISEASE (REFSUM'S DISEASE)

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

No. 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 or enzyme defect in phytanoyl-CoA hydrolase. 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.

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 can precipitate 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 8,000 μmol/L. A number of small case series and isolated reports have described clinical improvements in patient signs and symptoms with plasma exchange in conjunction with dietary control. TPE has been found to improve polyneuropathy, ichthiosis, ataxia, and cardiac dysfunction in most but not all patients treated. Unfortunately, as is also reported with dietary treatment alone, 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. Case reports and case series have used TPE to treat 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. In LDL apheresis, 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   **Frequency**: Daily for acute exacerbation; variable for chronic therapy
Replacement fluid: TPE: albumin; LDL Apheresis: NA

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 lifelong.

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POLYCYTHEMIA VERA; ERYTHROCYTOSIS

Incidence: PV: 0.9/100,000/yr; Prevalence: 0.3% secondary erythrocytosis	Indication	Procedure	Recommendation	Category
	Polycythemia vera	Erythrocytapheresis	1B	I
	Secondary erythrocytosis	Erythrocytapheresis	1C	III

No. of reported patients: > 300	RCT	CT	CS	CR
Polycythemia vera	0	3(225)	6(612)	0
Secondary erythrocytosis	0	29	6(307)	1(1)

Description of the disease

Absolute erythrocytosis is defined as a RBC mass of at least 25% above the gender-specific mean predicted value. Hct values >60% for males and >56% for females is indicative of absolute erythrocytosis, as these levels cannot be achieved with plasma volume contraction alone or other causes. Primary erythrocytosis refers to the MPD (myeloproliferative disease) PV, in which an abnormal hematopoietic stem cell clone autonomously overproduces RBCs. Additional features of PV include splenomegaly, granulocytosis, thrombocytosis and mutations of the tyrosine kinase *JAK2* (>90% of cases), as well as the tumor suppressor *TET2* mutation (22%). Secondary erythrocytosis refers to isolated RBC overproduction due to a congenital erythropoietic or hemoglobin defect, chronic hypoxia related to a respiratory or cardiac disorder, ectopic Epo (epogen) production, Epo administration, 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. Altered blood flow rheology increases the risk of thrombosis by pushing the platelets closer to the vessel edge, increasing vessel wall and von Willebrand factor interaction. Altered antifibrinolytic activity, clot resistance to fibrinolysis, endothelial dysfunction, and platelet function may account for the increased thrombotic risk, which is encountered in 15–40% of PV patients. Uncontrolled erythrocytosis (Hct > 55%), age > 60 years, history of prior thrombosis are considered high risk for thrombotic complications. The risk of transformation to myelofibrosis or acute myeloid leukemia is 3 and 10% 10-year risk, respectively.

Current management/treatment

Management of low risk PV includes phlebotomy, with the goal to maintain the Hct ≤45% and low dose aspirin. Phlebotomy results in iron deficiency, which decreases RBC overproduction. In PV associated with extreme thrombocytosis (platelet count > 1,000 × 10⁹/L) may be associated with increased bleeding risk due to acquired von Willebrand syndrome. High risk PV patients 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. In secondary erythrocytosis, treatment of the underlying cause is preferred; long-term supplemental oxygen and/or continuous positive airway pressure maneuvers for hypoxia; surgical interventions for cardiopulmonary shunts, renal hypoxia, or an Epo-producing tumor; ACE-I and A2R for post-renal transplantation erythrocytosis. When an underlying disorder cannot be reversed, symptomatic hyperviscosity can be treated by isovolemic phlebotomy.

Rationale for therapeutic apheresis

Erythocytapheresis, like isovolemic phlebotomy, corrects hyperviscosity by lowering the Hct, which reduces capillary shear, increases microcirculatory blood flow and improves tissue perfusion. Erythrocytapheresis reduces the Hct more efficiently than simple phlebotomy and can increase the interprocedural time and decrease the number of procedures needed to achieve the target Hct. The decision to use an automated procedure over simple phlebotomy should include consideration of the risks. For severe microvascular complications or significant bleeding manifestations, erythrocytapheresis may be a useful alternative to large-volume phlebotomy; particularly if the patient is hemodynamically unstable. Erythrocytapheresis prior to surgery can be used to reduce the high risk of perioperative thrombotic complications if Hct >55%. An RCT of 365 patients with PV (Marchioli, 2013) found that patients kept at a target Hct <45% compared to Hct 45–50% had significantly lower rate of cardiovascular death and major thrombosis. Although the study did not use automation, the target Hct appears to be the most important risk factor for undesirable outcomes. A study of 76 PV patients found platelet function improvement after erythrocytapheresis, as measured by TEG, suggesting that the hemodilution achieved with the procedure may reduce thrombotic risk. Thrombocytapheresis, as well as erythrocytapheresis, may be indicated for patients with PV with an acute thrombohemorrhagic event associated with uncontrolled thrombocytosis and erythrocytosis.

Technical notes

Automated instruments allow the operator to choose a post-procedure target Hct level and calculate the volume of blood removal necessary to attain the goal. A study (Bai, 2012) found that using exchange volume <15 mL/kg and inlet velocity <45 mL/min, especially for patients >50 years may decrease adverse events; Evers (2014) proposes a mathematical model for choosing most appropriate therapy parameters. During the procedure, saline boluses may be required to reduce blood viscosity in the circuit and avoid pressure alarms.

Volume treated: Volume of blood processed is based on TBV, starting Hct and desired post-procedure Hct.	**Frequency**: As needed for symptomatic relief or to reach desired Hct (usually one)
Replacement fluid: Albumin, normal saline	

Duration and discontinuation/number of procedure

In patients with PV, the goal is normalization of the Hct (< 45%). For secondary erythrocytosis, the goal is to relieve symptoms but retain a residual RBC mass that is optimal for tissue perfusion and oxygen delivery. A single procedure should be designed to achieve the desired post-procedure Hct.

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POST TRANSFUSION PURPURA

Incidence: 2/100,000 transfusions		Procedure TPE	Recommendation Grade 2C	Category III
# of reported patients: < 100	RCT 0	CT 0	CS 1(3)	CR 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) 5–10 days after transfusion of any blood component, usually RBCs in a multiparous female. Most commonly PTP occurs in patients whose platelets lack the HPA-1a platelet antigen and who have previously developed alloantibodies against HPA-1a due to immunization during pregnancy or blood transfusion. Other platelet alloantibodies have also been implicated. Clinical entities that should be excluded from the differential diagnosis include drug-induced thrombocytopenia (including heparin induced thrombocytopenia), immune thrombocytopenia, sepsis, and disseminated intravascular coagulopathy. The pathogenesis of PTP remains incompletely understood but it is clear that the patient destroys both transfused and autologous platelets. There are currently four hypotheses to explain the destruction of autologous antigen negative platelets observed in patients with PTP: (1) immune complex mediated platelet destruction via binding of the Fc receptor leading to platelet clearance; (2) soluble platelet antigens, possibly derived from platelet microparticles, passively transferred in the blood product which bind to the patients' platelets and provide a target for the alloantibody; (3) an alloantibody that also exhibits auto reactivity; and (4) an autoantibody which develops in conjunction with the alloantibody. The detection of alloantibodies (generally high titer) against HPA-1a, or other platelet antigens, supports the PTP diagnosis. These high titer antibodies can be detected for up to one year after the PTP episode. PTP is generally self-limited, with complete recovery in about 20 days, even in untreated patients. The mortality of PTP is 5–10%. PTP recurrence after future transfusion is uncommon.

Current management/treatment

The current treatment for PTP is administration of high dose IVIG (2/kg/day over 2–5 days), with a 90% response rate. IVIG may act 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. There is a single case report of response to splenectomy in a patient who was not responsive to IVIG, steroids or TPE.

Rationale for therapeutic apheresis

Removal of platelet alloantibodies by TPE decreases the antibody titer and may remove residual soluble alloantigen; thereby, increasing platelet survival and reversing the bleeding risk. Based on the limited case reports, TPE seems to shorten the duration of thrombocytopenia. If IVIG is not effective, TPE may be considered when hemorrhage is present.

Technical notes

Due to severe thrombocytopenia, the anticoagulant ratio should be adjusted accordingly. Typically the replacement fluid is albumin to avoid further exposure to HPA-1a antigen. However, in bleeding patients plasma may be given toward the end of procedure to maintain clotting factor levels.

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 non-cutaneous bleeding stops.

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PREVENTION OF RHD ALLOIMMUNIZATION AFTER RBC EXPOSURE

Incidence: 15% of US population is RhD negative	Indication Exposure to RhD positive RBCs	Procedure RBC exchange	Recommendation Grade 2C	Category III
No. of reported patients: <20	RCT 0	CT 0	CS 0	CR 6(8)

Description of the disease

RBC alloimmunization is a complication most commonly associated with RBC transfusion. Once formed, patients with RBC alloantibodies are at risk for future hemolytic transfusion reactions, and difficulty finding crossmatch compatible RBC units. For females, alloimmunization can also lead to hemolytic disease of the fetus and newborn (HDFN). HDFN causes fetal anemia, hyperbilirubinemia, and when severe enough, hydrops fetalis and fetal death. HDFN due to anti-D can have a severe clinical course.

In most instances, patients are transfused ABO and RhD compatible RBCs; RhD matching is to prevent alloimmunization. In the setting of life-threatening bleeding, or due to low inventory, protocols are in place to provide rapid RBC transfusion without knowledge of the patient's blood type. Because of the limited availability of RhD negative RBC units (15% of Caucasians, 8% of African Americans are RhD negative), these protocols usually involve the selection of Group O, RhD positive RBCs for males and older females (past the age of future pregnancy, typically >50 years) in an effort to preserve RhD negative RBCs units for females of childbearing potential.

There have been reports of RhD negative females receiving RhD positive RBCs transfusions, mostly in the setting of life-threatening hemorrhage following trauma. In order to mitigate the subsequent risk of anti-D formation in patients with potential long-term survival, several strategies have been tried, such as RBC exchange and/or administration of RhIg (Rh immunoglobulin).

Current management/treatment

The decision to attempt to remove and/or inactivate RhD positive RBCs by RBC exchange and RhIg, respectively, should be balanced with the known frequency of RhD alloimmunization. Modern retrospective studies have found the rate of RhD alloimmunization in RhD negative recipients following transfusion with RhD positive RBCs is 10–30%. This rate, in ill patients, is lower than the often cited historical rate of 80%, which was in healthy prisoners. Proceeding with therapy to prevent RhD alloimmunization after RhD positive RBC exposure should be based on the risks of the therapies balanced with the risk of alloimmunization and its risk of FDHN, and the likelihood and choice of future childbearing.

Several case reports are published about prevention of RhD sensitization following administration of a RhD positive RBCs to RhD negative female patient. All of the reports calculated the presumed RBC transfusion volume and used immune therapy (RhIg) to prevent the immune system from developing anti-D antibody. Most of the authors also used RBC exchange to remove the majority of RhD positive RBCs from circulation prior to RhIg. Based on data from RhIg use in pregnancy, treatment should be within 72 h. RhIg dose and route (IV versus IM) provided to affected patients has varied in the reports; 20 ug/1 mL RhD positive RBCs in this setting appears appropriate, although there is no specific guidance for this indication. Most of the patients did not show evidence of overt hemolysis, as is sometimes seen following RhIg therapy in RhD positive individuals for immune thrombocytopenia. Because of large RhIg doses used, authors have spaced doses out in 8-h intervals and several cases describe using normal saline to support the patient through the ensuing hemolysis. In several cases, there were reactions noted with RhIg administration including urticaria, achiness, and respiratory deterioration. The use of premedications with antihistamines and diuresis after normal saline bolus was found to be helpful.

Rationale for therapeutic apheresis

The goal of using RBC exchange in this setting is to reduce the circulating RhD positive RBC to level for which RhIg can be safely administered. When the quantity of circulating RhD positive RBCs is larger (usually ≥20% of circulating RBC volume), RBC exchange should be considered. Some reports describe using RBC exchange at far lower levels of circulating RhD RBCs. All of the case reports published whether using RBC exchange and RhIg or RhIg alone have included follow-up (weeks to 1 year) with no evidence of anti-D formation.

Technical notes

Some reports did not use RBC exchange, only RhIg. For RBC exchange, the target should be tailored to the dose of RhD positive RBCs received to achieve a target fraction of cells remaining that can be treated with RhIg therapy. Authors varied on approach on how much blood to exchange, 1 RCV was typical. In adult patients, the replacement volume of RBC units ranged from 8 to 10 units.

Blood volume replacement: 1–2 RCV	**Frequency**: Once
Replacement fluid: RBC units; leukocyte reduced, RhD negative	

Duration and discontinuation/number of procedures

One procedure should be adequate to decrease the circulating RhD positive RBCs quantity to a level that can be treated with RhIg administration.

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PROGRESSIVE MULTIFOCAL LEUKOENCHEPHALOPATHY ASSOCIATED WITH NATALIZUMAB

Incidence: 3.7/1000		Procedure	Recommendation	Category
		TPE	Grade 1C	I
# of reported patients: <100	RCT	CT	CS	CR
	0	0	4(49)	14(16)

Description of the disease

Progressive multifocal leukoenchephalopathy (PML) is a rare CNS demyelinating disorder in immunocompromised patients (HIV, lymphoma) or with the use of immune modulating therapy. The pathogenesis involves latent polyoma JC virus (JCV) reactivation in peripheral reservoirs that then invades CNS. Clinical manifestations are highly variable and commonly include motor, language, cognitive, and visual impairment. Seizures and paroxysmal events can occur at presentation, which helps differentiate PML from multiple sclerosis (MS) relapse. Demonstration of JCV DNA by ultrasensitive PCR in the CSF is diagnostic for PML.

Natalizumab, which is approved for highly active relapsing-remitting MS, is a humanized monoclonal antibody directed against the α4-subunit of α4β1 and α4β7 cellular adhesion integrins which blocks the binding of the α4-subunit (expressed on surface of circulating lymphocytes) to vascular cell adhesion protein, thus inhibiting adhesion and migration of lymphocytes into tissues including CNS. Its' MS specific activity relates to the blocking of very late antigen-4 (VLA-4)-mediated immune cell adhesion to endothelium of blood brain barrier (BBB). Thus, lymphocytes transmigration into CNS parenchyma via BBB is inhibited, leading to reduced inflammation.

Natalizumab associated PML might be due to compromised brain immune surveillance subsequent to the blockage of the lymphocyte transmigration. Mobilization of JCV carrying cells from the bone marrow was also suggested. Risk factors for increased incidence include JCV antibody seropositivity, prior immunosuppressive therapy, and longer duration of treatment (> 2 years). PML was also described, although less frequently, with other monoclonal antibodies (efalizumab, rituximab). Thus, heightened attention to PML in patients on this group of drugs is warranted. A standard system for defining diagnostic certainty of monoclonal antibody treatment-associated-PML was recently proposed based on clinical, imaging and laboratory findings.

Current management/treatment

Prevention of PML development with risk stratification approaches (drug holidays) are warranted. Immune reconstitution is the only intervention with demonstrated efficacy for PML once it develops. For natalizumab-treated patients, this includes discontinuation of the drug (temporary or permanent) and initiation of TPE to accelerate clearance. Both will increase number and function of leukocytes entering CNS. Based on in vitro data, mefloquine and mirtazapan has been given to limit viral replication.

Rationale for therapeutic apheresis

Natalizumab's long duration of action delays immune reconstitution. It has been suggested that its biologic half-life may be several times longer than its pharmacokinetics would predict. The pharmacokinetic half-life in MS patients is ∼11 ± 4 days; however, natalizumab is detectable in the circulation for ≤12 weeks and CSF cell counts are significantly reduced for ≤ 6 months. Furthermore, saturation of the natalizumab receptor is correlated with its serum concentration and it has been shown that mean α4-integrin saturation levels remain > 70% at 4 weeks after infusion. Khatri (2009) showed that serum natalizumab levels 1 week after final TPE were reduced by 92% (average) from baseline with 75 ± 28% reduction 4 weeks after natalizumab infusion when comparing same patients with and without TPE. Additionally, desaturation of the α4-integrin receptor to <50% was achieved when natalizumab concentration was <1 μg/mL (therapeutic level). Lastly, TPE significantly increased leukocyte transmigration ability in vitro. Thus, TPE accelerates removal of natalizumab, decreases receptor saturation, and restores leukocyte transmigration. The net result is to allow lymphocytes to adhere to vascular endothelium and rapidly restore immune function which may improve clinical outcomes.

Technical notes

Rapid immune reconstitution may precipitate an extreme immune response called Immune Reconstitution Inflammatory Syndrome (IRIS). IRIS usually develops 2–6 weeks after TPE (versus 3 months after drug discontinuation) in almost all patients. IRIS is associated with neurological status deterioration, often life-threatening. IRIS stems from massive influx of lymphocytes into the CNS following natalizumab clearance leading to renewed immune surveillance and increased inflammation. Abrupt worsening of neurologic symptoms in patients on natalizumab treated with TPE therefore most likely represent IRIS and not worsening disease course. The recommended treatment of IRIS is high-dose corticosteroids and NOT TPE. Because of the indirect implication of chemokine receptor 5-postive (CCR5+) T cells in IRIS pathophysiology, a recent CR described the successful use of maraviroc, a CCR5 antagonist, in prevention of IRIS in natalizumab-induced PML patient after TPE.

Some authors have superficially described the use of IA using the tryptophan polyvinyl alcohol column with TPE as possible alternative for TPE but no detailed experience of using it alone has been described.

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

Duration and discontinuation/number of procedures

In the pharmacokinetics study, three procedures of 1.5 PV were performed every other day. Modeling based on this study's results predicted that five TPE procedures would be needed for >95% of patients to lower natalizumab levels below therapeutic level. Five procedures were most commonly used in reported cases. One of the studies suggested utilizing pre and post TPE natalizumab levels with a target of < 1 μg/mL to guide therapy in order to optimize treatment.

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PRURITUS DUE TO HEPATOBILIARY DISEASES

Incidence: Rare	Indication	Procedure	Recommendation	Category
	Treatment resistant	TPE	Grade 1C	III
No. of reported patients: <100	RCT	CT	CS	CR
	0	0	2(7)	4(6)

Description of the disease

Chronic pruritus can present in patients with a variety of hepatobiliary disorders including: primary biliary cirrhosis (PBC), primary sclerosing cholangitis, cholangiocarcinoma, inherited cholestasis, and intrahepatic cholestasis of pregnancy. Cholestasis may be caused by hepatocellular secretory failure, bile duct damage or obstruction of the bile duct system. Up to 70–80% of patients with PBC and primary sclerosing cholangitis may experience pruritus, while pruritus is less seen in patients with obstructive cholestasis.

Pruritus may range from mild and tolerable, to difficult to tolerate, limiting daily life activities, causing severe sleep deprivation, depression, and even suicidal ideation. Itching tends to intensify during evening, limbs and, in particular, palms and soles have more severe pruritus but it can be generalized. However, no primary causing skin lesions are identified. For females, pruritus is affected by hormones, it is worse during the progesterone phase of the menstrual cycle, pregnancy, and hormone replacement therapy.

The pathogenesis of pruritus in cholestasis remains to be defined. Previously bile salts, endogenous μ-opioids, histamine, serotonin, and steroids were thought to be causing agents, but no firm correlation has been established. Recent studies have demonstrated that neuronal activator lysophosphatidic acid and autotaxin (an enzyme forming lysophosphatidic acid) correlate to the severity of pruritus and the treatment efficacy.

Current management

Medication therapy include: (1) first line: anion exchange resin colestyramine to remove the pruritogen(s) from the enterohepatic cycle in mild pruritus, (2) second line: rifampicin to modulate central itch and/or pain signaling, (3) third line: naltrexone (μ-opioid antagonist, modulate central itch and/or pain signaling), and (4) fourth line: sertraline (modulate central itch and/or pain signaling). For patients unresponsive to medications, other measures may be used: (1) nasobiliary and transcutaneous drainage or external biliary diversion to remove the pruritogen(s) from the enterohepatic cycle, (2) anion absorption, TPE, or extracorporeal albumin dialysis to remove the potential pruritogen(s) from the systemic circulation, and (3) liver transplantation.

Rationale for therapeutic apheresis

TPE may remove the potential pruritogen(s) from the systemic circulation. Out of 13 reported cases of patients with chronic pruritus due to hepatobiliary disorders, 10 (77%) responded to TPE. Patient may experience decreased pruritus after 2nd TPE. For some patients, the effect may last many months, while for others, chronic maintenance TPE is needed.

Technical notes

Volume treated: 1–1.5 TPV **Replacement fluid**: albumin	**Frequency**: 3 (weekly or biweekly) procedures initially then, 2–4 times per month for maintenance

Duration and discontinuation/number of procedures

Some may require long-term TPE, treatment is individualized based on patient's symptoms.

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PSORIASIS

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

No. of reported patients: 100–300	RCT	CT	CS	CR
Adsorptive cytapheresis	0	1(44)	4(25)	5(8)
Lymphocytapheresis	0	0	3(18)	0
ECP	0	1(52)	2(12)	0
TPE/cascade apheresis	0	1(6)	3(23)	0

Description of the disease

Psoriasis is a chronic skin disorder with high genetic predisposition. Plaques and papules are result of hyperproliferation and abnormal differentiation of 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 overall thickness of lesions (from thin- to thick-plaque spectrum). Increased number of tortuous capillaries leads to redness of 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 T cells transport from the dermis into epidermis as key event. Psoriatic T cells predominantly secrete interferon-γ and interleukin-17. Imbalance is further affected by a decrease in activity but not number of T reg and decreased levels of IL-10. Recirculation of 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.

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 (PASI score; 0–72) which evaluates three features of psoriatic plaque (redness, scaling, and thickness) and extent of involvement of each body area.

Current management/treatment

There are topical and systemic therapies. Therapy is generally dictated by disease severity, comorbidities, patient's pReferences, and adherence to treatment. Moderate to severe psoriasis is defined as 5–10% involvement of body surface area. Topical therapies include emollients, corticosteroids, topical vitamin D analogs (calcipotriene, calcitriol), topical retinoids, topical calcineurin inhibitors (tacrolimus, pimecrolimus), and 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 immunosuppression (cyclosporine). Recently, biologic agents are used more frequently. TNF-alpha inhibitors (etanercept, infliximab and adalimumab) and ustekinumab, human monoclonal antibody against IL-12 and IL-23, were approved for treatment of moderate–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.

Rationale for therapeutic apheresis

Methodology and rationale for different apheresis procedures has evolved with better understanding of disease pathophysiology. Few small studies showed that TPE, including cascade filtration, provides no benefit in the treatment of psoriasis. The rationale for these studies was removal of cytokines and putative "psoriatic factor," which at that time were considered contributory to the disease process; however this is not consistent with current understanding TPE.

Selective removal of leukocytes through adsorptive granulocyte and monocyte apheresis (granulocyte/monocyte column) provides for a reasonable pathophysiological justification especially in context of disseminated pustular psoriasis. In a recent study 15 patients received 5 treatments (1/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 similar effect to adsorptive column but no direct comparison study is reported. However, 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. The largest study examined 93 patients with psoriasis and psoriatic arthritis, and demonstrated that 49/52 (94%) patients in ECP treatment vs. 27/41 (66%) in the control group showed significant improvement in skin and arthritis manifestations. Several smaller studies showed variable response.

Technical notes

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: Typically, MNCs are obtained from processing 1.5 L of whole blood, but volume processed varies based on patient weight and HCT. 2-process method collects and treats MNCs obtained from processing 2 TBV	**Frequency**: Adsorption: 1/wk; Lymphocytapheresis: 1/wk; ECP: One cycle/week for 4 months and then tapering
Replacement fluid: Adsorption: NA; Lymphocytapheresis: NA; ECP: NA	

Duration and discontinuation/number of procedures

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

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ECP

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RED CELL ALLOIMMUNIZATION IN PREGNANCY

Incidence: 100/100,000 newborns/yr (US)	Indication	Procedure	Recommendation	Category
	Prior to IUT availability	TPE	Grade 2C	III
No. of reported patients: >300	RCT	CT	CS	CR
	0	0	13(307)	27(30)

IUT = Intrauterine transfusion

Description of the disease

Hemolytic disease of the fetus and newborn (HDFN, also termed erythroblastosis fetalis or hemolytic disease of the newborn) occurs when maternal plasma contains alloantibody against RBC antigen carried by the fetus. Maternal IgG crosses the placenta and causes hemolysis of fetal RBCs, leading to fetal anemia and when severe enough, hydrops fetalis and fetal death. Most frequently severe HDFN is secondary to anti-D but it can be caused by a variety of RBC alloantibodies (antibodies to K, C, PP1Pk, E, and M). RBC alloimmunization usually occurs after fetomaternal hemorrhage or RBC transfusion. 0.1 mL of fetal RBCs can result in Rh sensitization. Severity of HDFN usually increases with subsequent pregnancies. Prophylactic Rh immunoglobulin during pregnancy and post-partum has greatly reduced HDFN incidence secondary to anti-D.

Current management/treatment

The following describes management of pregnant woman with newly identified clinically significant RBC alloantibody. (1) Patient history to identify source of exposure, such as previous pregnancy or transfusion. (2) Presumed father is RBC typed to assess for risk of fetal inheritance. If the father does not carry RBC antigen, then no further work up is needed. If father expresses antigen, further testing determines whether the father carries one or two copies of the gene. For most blood group antigens, serology can be used to determine paternal predicted genotype. For RhD, paternal zygosity must be determined genotypically. If the father is homozygous, fetus is at risk, if he is heterozygous, then fetal genotyping can be done. (3) Sensitized pregnancies are monitored by middle cerebral artery (MCA) Doppler ultrasound (velocimetry) to detect fetal anemia along with RBC antibody titer (higher titer, more severe HDFN). Critical titer thresholds are typically 8–32. Titers below critical threshold should be followed at scheduled prenatal obstetrics visit. Anti-K (Kell) suppresses RBC production and causes hemolysis, and antibody titers are not as predictive as for other antibodies. (4) If titers are > critical threshold or have increased by two dilutions from previous sample, serial ultrasound examinations should be performed. Most institutions use ultrasound with velocimetry as early as 18 week gestational age (GA) to determine fetal care rather than depend on antibody titration. Moderate–severe anemia is predicted when MCA measurement is > 1.5 multiples of the median (MoM), then intervention is needed. (5) Once this occurs cordocentesis is done to assess fetal Hct; if <30%, intrauterine transfusion (IUT) is needed. IUT usually cannot be technically performed until about 20 week GA. IUT uses RBCs negative for antigen against which maternal antibody is directed. Fetal mortality related to IUT is 1–2%. IUT can be repeated until fetus is ready for delivery; frequency of IUT depends on GA, final Hct at time of previous IUT, and number of prior transfusions. (6) Amniocentesis for fetal lung maturity assessment is used to determine whether fetus can be safely delivered. (7) After delivery, HDFN can result in neonatal hyperbilirubinemia, which can cause kernicterus and permanent brain damage. Therefore post-delivery, neonate must be closely monitored to prevent and treat hyperbilirubinemia. Infants with HDFN can have hypoproliferative anemia that require careful monitoring for several weeks post delivery and potentially need transfusions.

If the fetus is known to be at high risk for hydrops fetalis based on ultrasound or previous prenatal loss, or high titer antibody in early pregnancy, 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 <20 week, then TPE and/or IVIG may be indicated.

Rationale for therapeutic apheresis

TPE removes maternal RBC alloantibody. TPE may decrease maternal antibody titer and amount of antibody transferred to fetus, thereby decreasing RBC destruction and improving HDFN disease. Survival in severe cases with the use of TPE and/or IVIG prior to IUT is ~75%. The majority of CRs and CSs patients have anti-D or other Rh antibody. Typically, IUT can be performed after the fetus reaches 20 week GA.

Technical notes

TPE can safely be performed during pregnancy. Blood and plasma volumes increase as pregnancy progresses. In the second or third trimester, the patient should lay on her left side to avoid compression of inferior vena cava by gravid uterus. Hypotension should be avoided as it may result in decrease perfusion to the fetus.

Volume treated: 1–1.5 TPV	Frequency: 1–3/week
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

TPE should be considered early in pregnancy (7–20 week) and continued until IUT can safely be administered (~20 week GA). 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 12 week GA followed by weekly IVIG (1 g/kg) until 20 week GA (Ruma, 2007).

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RENAL TRANSPLANTATION, ABO COMPATIBLE

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

No. of reported patients: > 300	RCT	CT	CS	CR
AMR	3(61)	8(342)	37(727)	13(14)
Desensitization	0	5(441)	29(466)	11(11)
High PRA	0	0	1(20)	0

AMR = antibody-mediated rejection; DD= deceased donor; HLA= human leukocyte antigen; LD= living donor; PRA = panel reactive antibodies

Description of the disease

Use of immunologically incompatible kidneys is growing as a response to organ shortage and increased sensitization among recipient candidates. HLA antibodies may be directed to donor-specific angiten (DSA). HLA antibodies result from previous exposure to foreign HLA Ag during transfusions, pregnancy, or transplantation and are barrier to transplantation because of increased risk for graft loss secondary to hyperacute, acute, or chronic antibody mediated rejection (AMR). Additionally, patients with elevated HLA antibody screen (high PRA) have difficulty finding HLA compatible donor and remain on the transplantation list significantly longer than unsensitized patients. TPE and IA are now used in many transplant centers, to broaden access to transplantation through desensitization, lowering pre-existing antibody titer.

AMR has emerged as a leading cause of early and late allograft injury. Diagonsis is based on Banff classification and relies on (1) DSA detection 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 include those with previous transplant and high PRA. Subclinical AMR leads to chronic humoral rejection and late graft loss.

Current management/treatment

New immunosuppressive drugs are continually being developed to prevent and treat acute renal allograft rejection, and to decrease antibody titers. Transplant recipients are placed on immunosuppressive therapy (cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine, antithymocyte globulin).

Desensitization regimens typically include IVIG, rituximab, ± additional immunosuppression. Desensitization protocols use low or high dose IVIG, TPE or IA, and/or rituximab to convert positive to negative crossmatch and enable transplantation. Bortezomib, a protease inhibitor used to target plasma cells, has been added to some protocols and seems to be effective in treatment of refractory AMR, but results were not promising in desensitization. TPE-based regimens appear to be effective for those awaiting living donor transplants. Transplant after desensitization of high PRA patients has also been performed within context of kidney paired donations (KPDs; "kidney swaps") and such matching is expected to increase. A recent multicenter study ($n = 1,025$) demonstrated higher survival rate at 1, 3, 5, and 8 years posttransplant in recipients from incompatible donors when compared to patients who either did not undergo transplant or those who waited for transplant from deceased donor.

AMR treatment has evolved from IVIG to combination regiments using TPE or IA, IVIG, and rituximab. Clinical trials have demonstrated improved graft survival with TPE+IVIG versus TPE alone or IVIG alone, and TPE + rituximab versus TPE alone. A recent non-randomized study compared high-dose IVIG with TPE+IVIG+ rituximab and showed both better graft survival and lower DSA levels posttransplant with the latter. However, use of rituximab has been associated with increased rates of infection.

Rationale for therapeutic apheresis

In AMR, DSA can be removed with TPE, DFPP, and IA. Apheresis is always performed in combination with other immunosuppressive drugs. RCTs 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. CSs since 1985 have shown improvement when TPE is used in patients with acute vascular rejection in combination with a variety of anti-rejection medications. This is likely due to improved anti-rejection medications, improved DSA detection, and improved AMR definition using Banff criteria. Previously there was a high graft loss rate with acute vascular rejection; current regimens that 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, DFPP, or IA is used in combination with immunosuppressive drugs pre-transplant until crossmatch is negative. TPE is usually continued postoperatively and re-initiated if AMR occurs. Ability to obtain negative crossmatch depends on DSA titer. Using ∼5 TPE pre-operatively will allow the titer of ≤32 to become negative. AMR risk is ∼40% with ∼90% 1 year graft survival. Desensitization protocols are appropriate in carefully selected patients.

Technical notes

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 post-operatively for a minimum of three procedures. Further treatment is determined by risk of AMR, DSA titers, or the occurrence of AMR.

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RENAL TRANSPLANTATION, ABO INCOMPATIBLE

Incidence: Infrequent	Indication	Procedure	Recommendation	Category
	Desensitization, LD	TPE/IA	Grade 1B	I
	Antibody mediated rejection	TPE/IA	Grade 1B	II
	A_2/A_2B into B, DD	TPE/IA	Grade 1B	IV
No. of reported patients: > 300	RCT	CT	CS	CR
	0	0	>21 (>755)	>28(>45)

DD = deceased donor; LD = live donor.

Description of the disease

Due to a relative shortage of compatible organs for renal transplantation, ABO incompatible (ABOi) living donors are used. Greater than 100,000 candidates are on the United Network for Organ Sharing (UNOS) waiting list to receive renal allograft. In 2014 (US), 15,500 renal transplants were performed with 32% of patients received kidneys from live donors. Major incompatibility refers to the presence of natural antibodies in recipient against donor's A or/and B blood group antigen. These antibodies may cause hyperacute/acute humoral rejection causing endothelial damage (A and B antigens are expressed on vascular endothelium). Major ABOi exists in ~35% of random donor–recipient pairs.

Current management/treatment

Most published reports on ABOi solid organ transplantations involve TPE-mediated removal of anti-A or anti-B in conjunction with immunosuppressive treatment (tacrolimus, mycophenolate mofetil, prednisone, daclizumab, rituximab, bortezomib, and eculizumab). Other immunotherapy modalities including IVIG and antithymocyte globulins have important roles in the transplant process. Splenectomy, while formerly considered an absolute requirement for ABOi renal transplantation, is no longer necessary. However, it continues to be helpful in the setting of severe refractory rejection. Recently published case reports have used rituximab/eculizumab/bortezomib in ABOi renal transplantation, both prophylactically and treating rejection, but their use varies, and there are no universally accepted protocols for their use. A, B, and AB donor organs have been successfully transplanted with these desensitization strategies. One recent report (Masterson, 2014) suggests that TPE may not be necessary in live donor ABOi renal transplantation if the baseline levels of ABO antibodies are low; however this approach requires replication in larger studies. ABOi renal transplantation has also been performed within the context of kidney paired donations (KPDs; "kidney swaps") and such matching is expected to increase due to disproportionately long wait times for O recipients. BK virus associated nephropathy (BKVAN) is also a concern in patients receiving ABOi renal transplants and periodic BK virus monitoring is recommended.

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 in group O or B recipients in living donor kidney transplantation as they have a lower risk of graft rejection. UNOS permits A_2/A_2B deceased donor kidney transplantation into B recipients if certain anti-A 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 use the of TPE to facilitate ABOi renal transplantation, abundance of supportive evidence exists. Given that hyperacute rejection and acute antibody mediated rejection are risks in ABOi renal transplants, TPE has been used as key therapeutic modality to reduce anti-A and/or anti-B titers in peri-transplant period with goal of preventing rejection and facilitating graft survival. Both short- and long-term ABOi kidney transplant survival statistics compare well with that seen in ABO-compatible transplants. In ABOi kidney transplantation, TPE is used to lower antibody titers below a critical threshold (which differs based on titration method/technique) prior to the transplant procedure. Apart from TPE, DFPP and ABO-antigen specific and non-specific IA columns have been used (outside the US) to remove ABO antibodies.

Technical notes

The replacement fluid for TPE is albumin or plasma (plasma should be compatible with both the recipient and donor ABO type), depending upon the presence of coagulopathy. In the immediate pre/post surgical setting, plasma is typically used. Lentine (2014) reported a higher incidence of early bleeding complications among ABOi renal transplant patients, and close monitoring of coagulation status is recommended.

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 critical threshold prior to taking patient to transplant. It is important to note that this threshold titer will need to be determined by each program, given that titer results can vary widely depending on titration method and technique used. The number of TPE procedures required depends upon baseline IgG titer, and on rate of antibody production/rebound. Most AMR episodes occur within the first 2 weeks following transplantation. Post transplant ABO titers have low positive predictive value and high negative predictive value for diagnosis of AMR (Tobian, 2010). Several ABOi programs utilize biopsies to monitor the allograft for histological signs of rejection prior to TPE discontinuation, although this practice is not universal. Of note, C4d positivity is very common in ABOi transplant renal biopsies; however this is not necessarily indicative of humoral rejection unless accompanied by light microscopic changes suggestive of rejection.

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SCLERODERMA (SYSTEMIC SCLEROSIS)

Incidence: 9–19/1,000,000/yr; 9:1 (F:M)		Procedure	Recommendation	Category
		TPE	Grade 2C	III
		ECP	Grade 2A	III

No. of reported patients: > 300	RCT	CT	CS	CR
TPE	0	3(75)	7(70)	20(21)
ECP	3(162)	0	5(87)	NA

Description of the disease

Systemic sclerosis (SSc) is a systemic connective tissue disorder of unknown etiology characterized by the accumulation of collagen and other extracellular matrix proteins, in skin and other organs. Antinuclear antibodies are present in more than 95% of patients with SSc. The limited cutaneous form (distal extremities and face only) usually presents with features of CREST (Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia). The diffuse cutaneous form is characterized by thickening of the skin (scleroderma) and progressive visceral organ dysfunction due to fibrosis [e.g., lungs (interstitial fibrosis), heart, liver (biliary cirrhosis), and/or kidneys (renovascular hypertensive crisis]. The pathophysiology implicates cell-mediated immunity involving activated T cells including Th-17, 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

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. Calcium channel blockers may provide symptomatic relief of Raynaud's phenomenon. ACE inhibitors have dramatically improved the poor outcome of renal hypertensive crisis. Newer treatment modalities include the use of minocycline, PUVA, lung transplantation, etanercept, and thalidomide. However, no medications appear to be truly effective in patients with aggressive disease. The role of T cells in pathophysiology leads to increased interest in targeted therapies such as basiliximab, alemtuzumab, and abatacept.

Rationale for therapeutic apheresis

TPE has been used for SSs since the 1980s with the rational that humoral factors might play an important role in the pathogenesis. A controlled trial of 23 patients randomized to no apheresis, TPE, or lymphoplasmapheresis showed statistically significant improvement in skin score, physical therapy assessment, and patient and physician global assessment in both treatment groups. Long-term TPE (2–3 weekly for 2 weeks, 1 TPE weekly for 3 months, and 1 TPE every other week as a maintenance therapy) was also evaluated in a controlled trial. All serological markers improved in comparison to the control group; however, there was no difference in clinical outcomes. In a case series reporting on 15 patients who received TPE in combination with prednisone and cyclophosphamide (Dau, 1981), 14 patients had clinical improvement. In a case series of scleroderma renal crisis (Cozzi, 2012), adding TPE to ACE inhibitors in patients who developed microangiopathy or were intolerant to high dose of ACE inhibitors showed preservation of renal function sufficient to avoid dialysis as well as improved 5-year survival rates.

ECP (2 treatments every month) was used in the treatment of scleroderma in a sham RCT of 64 patients. The study was statistically underpowered to reveal significant differences between the two study arms. However, serial measurements within each group showed significant improvements in skin scores and mean joint involvement after 6 and 12 months in the ECP group but not in the sham group. An earlier multicenter RCT of 79 patients with recent onset disease also showed a statistically significant improvement in skin and joint parameters at 6 months among 68% of ECP treated patients compared to 32% on D-penicillamine. In contrast, a randomized crossover study of 19 patients comparing ECP with no treatment revealed no statistical difference in skin scores after 1 year of treatment. A recent case series of 16 patients treated with 12 ECP procedures (two consecutive days every 6 weeks) reported decreased dermal thickness and increased joint mobility. Immunomodulatory effects were followed in this series and showed a decrease in Th-17 as well as a shift from pro- to anti-inflammatory and anti-fibrotic cytokines. In a long-term follow-up study from the same group, those immunomodulatory effects of the ECP treatment last for 1 year only.

Technical notes

Volume treated: TPE: 1–1.5 TPV; ECP: Typically, MNCs are obtained from processing 1.5 L of whole blood, but the volume processed may vary based on patient weight and HCT. The 2-process method collects and treats MNCs obtained from processing 2 TBV.
Replacement fluid: ECP: NA; TPE: Albumin

Frequency: TPE: 1–3/wk; ECP: Two procedures on consecutive days (one series) every 4–6 wk for 6–12 months;

Duration and discontinuation/number of procedures

TPE courses vary widely. A course of six procedures over the 2–3 weeks should constitute a sufficient therapeutic trial. In the scleroderma renal crisis study, TPE was discontinued when sufficient renal function (CR< 300 μmol/L and serum urea < 15 mmol/L) remained stable for at least one month or when the patient required dialysis. ECP course is longer; at least 6 months trial should be considered. If no response is noted, ECP treatment intervals should be increased or stopped completely.

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SEPSIS WITH MULTIORGAN FAILURE

Incidence: 300/100,000/yr (US)		Procedure TPE	Recommendation Grade 2B	Category III
No. of reported patients: >300	**RCT** 4(194)	**CT** 5(155)	**CS** 12(231)	**CR** 11

Description of the disease

Sepsis is a systemic inflammatory response to infection in which multiple toxic mediators cause tissue injury, multiple organ dysfunction (MODS), often with disseminated intravascular coagulopathy (DIC), and relative immunosuppression. It is the most common cause of death in non-coronary intensive care units with mortality rate of 28–50%, 70% with MODS. It is the 10th most common cause of death in the US and accounts for 2–3% of all hospital admissions. The incidence of sepsis is compounded by the emergence of antimicrobial resistant bacteria. 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. Cytokines and other mediators in sepsis include tumor necrosis factor (TNF), interleukins, leukotrienes, prostaglandins, endotoxin, and TGF-β are part of the inflammatory state. Coagulopathy, microvascular occlusion, and tissue ischemia appear to be connected to derangements in the balance of ADAMTS13 and von Willebrand factor multimers.

Current management/treatment

Management includes antimicrobial agents and control of the source of the infection, hemodynamic support including volume and vasopressors and ventilator support. Additional treatments include corticosteroids, monoclonal antibodies to TNF, soluble TNF receptor, antithrombin, and tissue factor pathway inhibitor, although there is not broad acceptance of any one of these therapies. Importantly, continued research and additional therapies are being sought.

Rationale for therapeutic apheresis

TPE is postulated to improve organ function by removing inflammatory and antifibrinolytic mediators and replenishing anticoagulant proteins and ADAMTS13, in an effort to reverse the pathobiological derangement and restore hemostasis. Observational 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, and that TPE may lead to hemodynamic stabilization. A retrospective cohort in 42 pediatric patients found an improvement in 28-day mortality, after controlling for illness severity.

Unlike the observational studies suggestion of efficacy, prospective randomized studies have been conflicting. Four RCTs of 10–106 patients each using TPE have been published. The largest RCT by Busund (2002) employed a single TPE with one additional TPE the next day if there was no improvement. The authors found a 28-day mortality rate of 33% in the treatment and 53.8% in control ($P < 0.05$). When controlled for other contributing factors, the significance of the effect of TPE on mortality became a non-significant trend ($P = 0.07$). One RCT (Reeves, 1999) used continuous plasma filtration in 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. In a 48 patient RCT of adults and children which compared plasma filtration to standard therapy, there was no significant difference in 28-day mortality; the study closed early due to poor enrollment. One RCT (Nguyen, 2008) enrolled 10 children with thrombocytopenia associated multi-organ failure (TAMOF) and culture positive sepsis and randomized them 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 (1/5 survived in control group, 5/5 survived in treatment group, $P < 0.05$) was seen in the TPE treated group, who received median of 12 days of TPEs, leading to the trial being stopped early due to improvement in treatment group. Although two of four studies did not meet enrollment, making interpretation difficult, they were collectively analyzed in a meta-analysis; no association with overall mortality was found with TPE. There was an association for decreased mortality in the adult subgroup (not pediatric), suggesting a relatively high likelihood of bias. Another meta-analysis that encompassed all of blood purification techniques found decreased mortality as well, but the analysis included various approaches including hemofiltration, hemoperfusion and TPE, making it difficult to draw conclusions from the pooled data set.

Technical notes

Centrifugal-based and filtration-based instruments have been used. In addition to TPE, 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 TBV daily for four days. Neither of these devices has been approved for use in the US. Because these patients are severely ill with hypotension and cardiovascular instability, treatment is performed in the intensive care unit. A study (Dyer, 2014) has been published describing the use of tandem procedures in line with extracorporeal membrane oxygenation, especially in pediatrics.

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

Duration and discontinuation/number of procedures

Busund (2002) limited treatment to 1–2 TPE. Nguyen 2008 performed up to 14 TPE.

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SICKLE CELL DISEASE, ACUTE

Incidence: 273/100,000 African-Americans(1/375 for Hb SS, 1/835 for Hb SC, 1/1667 for Hb S/β-thalassemia live births); 89.8/100,000 Hispanics primarily from Caribbean islands	Indication	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
No. Reported patients: $>300^a$	**RCT**	**CT**	**CS**	**CR**
Acute stroke	0	1(52)	7(160)	8(10)
Acute chest syndrome	0	2(121)	13(145)	8(8)
Priapism	0	0	1(5)	1(1)
Multisystem organ failure	0	0	3(10)	3(3)
Hepatic sequestration/intrahepatic cholestasis	0	0	1(52)	3(4)
Splenic sequestration	0	0	3(204)	0

[a]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) is caused by abnormal sickle hemoglobin (HbS) that is formed by the substitution of valine for glutamic acid at β6. HbS polymerizes upon deoxygenation, causing RBC to become rigid and deformed; sickled RBCs occlude the microvasculature leading to tissue hypoxia and infarction. HbS RBCs have a shortened lifespan (∼10–20 days), resulting in chronic hemolytic anemia. The overall mortality rate from SCD is 2.6% with the peak at 1–3 year. The average life expectancy is ≥50 years. The leading causes of death are sepsis, acute chest syndrome (ACS), stroke, acute multiorgan failure (MOF), and pulmonary hypertension. The use of penicillin has increased life expectancy.

Acute manifestations of SCD are vaso-occlusive crisis (VOCs), including stroke, ACS, priapism, splenic sequestration, hepatic/cholestatic, and renal dysfunction. In the absence of preventative therapies, ischemic stroke can occur in up to 10% (overt stroke) or 20–35% (silent stroke) of patients, with a recurrence rate of 46–90%. Patients of HbSS and HbSβ^0 are at the highest risk. ACS is defined by sudden decreased oxygen saturation despite oxygen therapy in the setting of new infiltrate on chest X-ray, often accompanying fever, tachypnea, coughing, and chest pain. The incidence is highest in young children (2–5 years). ACS is likely due to RBC sickling in the pulmonary vascular space; it can be idiopathic or associated with infection, pulmonary infarction, or fat embolism. Priapism (painful sustained erection > 4 h) can affect up to 35% of male SCD patients. Other acute manifestations of SCD are MOF and transient red cell aplasia (RCA).

Current management/treatment

Primary and secondary stroke prevention has resulted in marked stroke rate reduction, but residual risk exists. When patients present with signs of neurologic or mental status changes, CT/MRI/MRA should be urgently performed. If stroke is confirmed, emergent RBC exchange should be performed. The treatment for ACS comprises of supportive care including antibiotics (cephalosporin, macrolide), oxygen (target ≥95% SaO$_2$), and close monitoring. If Hb level is ≥1 g/dL below baseline and <9g/dL, transfuse RBCs. For rapid symptom or clinical progression (SaO$_2$ ≤90%), perform an emergent RBC exchange. Priapism should be treated with vigorous hydration and analgesia and consultation with urologist if symptoms do not improve. RBC transfusion may be used pre-operatively if surgical intervention is needed. Small studies have reported that RBC exchange resolved priapism within 24–48 h. MOF presents as unexpected life threatening VOC involving the lung, liver, and kidney. Management includes expedient evaluation and support of vital functions, and RBC transfusion or exchange. Hepatic sequestration and intrahepatic cholestasis management includes hydration and surgical consult, and simple transfusion or RBC exchange. In these cases, RBC transfusion or exchange resulted in a better outcome.

Rationale for therapeutic apheresis

The decision to use RBC transfusion, manual or automated RBC exchange is guided by the balance of patient's condition, and ability to obtain apheresis services, adequate intravenous access, and blood products quickly, versus the risk of apheresis itself. RBC exchange offers more efficient and rapid removal of HbS RBCs, and keeps the patient isovolumic. For patients with their first stroke, exchange (manual or automated) appears to result in a lower rate of stroke recurrence compared to those treated with RBC transfusion (21% (8/38) vs. 57% (8/14), respectively). A retrospective review of 81 pediatric patients with ACS found that therapy with RBC exchange in the children with worse pulmonary function equalized them to achieve a similar trajectory of care (hospital course) to those children with less severe pulmonary function at the start of the admission. The side effects of RBC exchange include central venous catheter thrombosis and hemorrhage, which can be mitigated with placement in internal jugular site compared to the femoral vein location, and hyperhemolysis.

Technical notes

Apheresis equipment calculates the replacement RBC volume to achieve the desired target HbS (fraction of patient's RBCs remaining at end of procedure) and Hct. General guidelines are: (1) end Hct at 30 ± 3% (≤33–36% to avoid hyperviscosity) and (2) HbS of 30% (or HbS + HbC of 30%, etc.). Patients with unstable blood pressure may not tolerate RBC exchange.

Volume treated: Volume necessary to achieve target HbS level **Frequency**: One procedure
Replacement fluid: RBC units, HbS negative, leukocyte reduced, antigen-matched (e.g. C, c, E, e, K)

Duration and discontinuation/number of procedures

For an acute situation, typically one procedure is necessary to achieve desired HbS level.

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SICKLE CELL DISEASE, NON-ACUTE

Incidence: 273/100,000 African-Americans(1/375 for Hb SS, 1/835 for Hb SC, 1/1667 for Hb S/β-thalassemia live births); 89.8/100,000 Hispanics primarily from Caribbean islands	Indication	Procedure	Recommendation	Category
	Stroke prophylaxis/iron overload prevention	RBC exchange	Grade 1A	I
	Recurrent vaso-occlusive pain crisis	RBC exchange	Grade 2C	III
	Pre- operative management	RBC exchange	Grade 2A	III
	Pregnancy	RBC exchange	Grade 2C	III

No. Reported patients: >300[a]	RCT	CT	CS	CR
Stroke prophylaxis/iron overload prevention	2(326)	1(36)	20(335)	3(3)
Vaso-occlusive pain crisis	1(130)	1(21)	3(18)	1(1)
Pre-operative management	3(1035)	4(184)	3(957)	0
Pregnancy	0	2(38)	1(5)	0

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

Description of the disease

Chronic complications can begin in early age. These include recurrent vaso-oclusive crisis (VOC), end-organ damage, avascular necrosis of bones, cholelithiasis, and complication from blood transfusions such as iron overload and alloimmunization. Chronic VOC (> 3 months) occurs in up to 55% of SCD patients.

Current management/treatment

RBC transfusion is one of the mainstays of long-term SCD therapy, and supported by multiple RCTs. For stroke prevention there are several important studies. The STOP trial randomized children with elevated blood flow velocity that denotes stroke risk to standard care without transfusion (control) versus chronic monthly transfusion for primary stroke prevention. The trial was terminated prematurely due to the marked (90%) stroke risk reduction by chronic transfusion. Another trial found that chronic RBC transfusion also was efficacious in secondary stroke prevention/progression in children with evidence of silent cerebral infarct on MRI imaging. Transfusion withdrawal is associated with an increased risk of recurrent stroke. During long-term therapy, targeting a pre-transfusion threshold of 50% HbS may be as effective as 30% HbS. Several studies have also shown decreased frequency of recurrent VOC with monthly manual RBC exchange transfusion.

Surgery is associated with high rates (up to 19%) of SCD related complications. The TAPS RCT demonstrated that pre-op transfusion was associated with decreased perioperative complications (39% non-transfused versus 15% transfused). Pre-op transfusion should target Hb of 10 g/dL. For patients with high baseline Hb such as in HbSC or HbSβ$^+$, RBC exchange may be used to avoid elevated blood viscosity, especially for high risk procedures (neurosurgery, prolonged anesthesia, cardiac bypass procedures).

Hydroxyurea, which increases HbF levels, is another mainstay of SCD therapy. Hydroxyurea reduces frequency of VOC episodes, ACS, and other severe complications, and is associated with less transfusion and hospital admissions. In pediatric patients with previous stroke, the SWiTCH RCT showed chronic RBC is not adequately replaced with hydroxyurea plus phlebotomy to prevent future stroke. Hematopoietic stem cell transplantationis a potentially curative therapy, however, indications and appropriate regimens are still being defined to optimize outcomes.

Rationale for therapeutic apheresis

Several observational studies have shown that automated RBC exchange yield a more efficient removal/replacement of HbS RBCs than manual exchange or RBC transfusions. RBC exchange may also have beneficial effects on blood viscosity, elasticity, and relaxation time, and reduction of adhesion molecule level like sVCAM-1. Although iron overload can be treated with chelation, its effectiveness has been limited by poor compliance. RBC exchange can remove, or keep iron stores steady (RBC exchange can result in iron overload if post- is set higher than pre-Hct). In a case series with 14 patients receiving chronic RBC exchange and 7 receiving chronic simple transfusion, RBC exchange was shown to have reduced iron overload, but increased donor exposure. In 36 pediatric patients, long-term RBC exchange for a mean of 5 years was associated with improved growth velocity without increased risk of iron overload compared to matched controls.

Chronic RBC exchange has also been described in several other clinical settings. In pregnancy, RBC transfusion, and sometimes, RBC exchange, had been reported to be associated with lower risk of maternal and neonatal mortality, intrauterine growth restriction and other fetal complications, and decreased rate of maternal complications, although larger comparative studies are needed. Careful fetal monitoring is recommended during RBC exchange (perinatal hydroxyurea is contraindicated). RBC exchange has also been used to manage pulmonary hypertension (with or without leg ulcers) improving feelings of breathlessness, SaO$_2$, and ability to execute activities of daily life. It has has also been described for prevention of progression of retinopathy.

Technical notes

Apheresis equipment calculates the replacement RBC volume to achieve the desired target HbS (fraction of patient's RBCs remaining at end of procedure) and Hct. General guidelines are: (1) end Hct at 30 ± 3% (≤33–36% to avoid hyperviscosity) and (2) HbS of 30% (or HbS + HbC of 30%, etc.). 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 potentially donor exposure. Patients with unstable blood pressure may not tolerate RBC exchange. Vortex ports have been used successfully in adults, with evidence of longer procedural duration and more complications than temporary central venous catheter. Long-term blood donor exposure can potentially increase the risk of of infecious transmission and RBC alloimmunization.

Volume treated: Volume necessary to achieve target HbS level
Replacement fluid: RBC units, HbS negative, leukocyte reduced, antigen-matched (eg. C, c, E, e, 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; one time for pre-op, variable times for chronic pain, and life-long for stroke prevention.

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STIFF-PERSON SYNDROME

Incidence: 0.1/100,000		Procedure TPE	Recommendation Grade 2C	Category III
No. of reported patients: < 100	**RCT** 0	**CT** 0	**CS** 5(30)	**CR** 13(14)

Description of the disease

Stiff-person syndrome (formerly known as stiff-man 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 an 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. Childhood onset as early as one year of age has been reported. 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 the serum in up to 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, anti-anxiety 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. Other immunosuppressive treatment, such as rituximab, has been tried with variable effect.

Rationale for therapeutic apheresis

The association of specific autoantibodies with stiff-person syndrome has led to scattered case reports, both with positive and negative results, and a few small case series describing responses to TPE in conjunction with other immunosuppressive therapies. There are no randomized trial data. Relatively small exchange volumes (2–3 L) have been employed, possibly compromising the potential effectiveness of treatment. One case report demonstrated the association between the decline of Ab level and the timing of TPE and its treatment response (Farooqi, 2015). In all 44 patients who received TPE, 59% had some degree of response.

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 TPEs of 1–1.5 TPV 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. Successful use of TPE for chronic treatment has also been reported.

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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

No. 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 ≤ 3 days. It has equal gender distribution and wide age distribution (average 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 blood supply to 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 them is associated with recovery. Additionally, elevated blood cholesterol levels lead to elevated cholesterol within perilymph of the cochlea, which 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 corticosteroids followed by corticosteroid taper or intra ear steroid injection is used to treat possible inflammation. Pentoxifylline is given to improve RBC flexibility and reduce blood viscosity. Intravenous dextran, hydroxyethyl starch, or glycerol is administered 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 is possible with apheresis. However, recent meta-analysis of six case–control studies revealed no association between lipid levels and SSHL. Another study demonstrated no relationship between fibrinogen and recovery in patients treated with heparin-induced extracorporeal LDL (HELP) apheresis.

Three RCTs evaluated HELP apheresis in treating SSHL. A trial of 27 patients (Suckfull, 1999) found greater hearing recovery at 24 h and 6 weeks with HELP (not statistically significant). A trial of 201 patients (Suckfull, 2002) found similar results, improved hearing but not statistically different. Final trial (Bianchin, 2010) examined standard therapy plus HELP (72 patients) 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 four frequencies was seen in standard treatment plus HELP group at 24 h (75% vs. 41%) and 10 days (76% vs. 45%). CS of 217 patients (Heigl, 2009) who failed to respond to standard therapy examined HELP as salvage therapy. Improvement was seen in 61% with time between onset of hearing loss and HELP treatment determining response; response rate declined by 71% if treatment occurred > 2 weeks after symptom onset.

A multicenter RCT comparing rheopheresis (93 patients), corticosteroids (40 patients), and hemodilution (59 patients) found all three equally efficacious (Mosges, 2009). The rheopheresis group had a higher quality of life score on a standardized questionnaire, likely due to limited course of therapy (1–2 treatments) compared to 10 days of infusion. 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. CS of 25 patients who failed standard therapy (Uygun-Kiehne, 2010) found a 68% improvement (40% complete hearing recovery and 28% partial recovery) following two rheopheresis procedures.

Fibrinogen selective columns were used in a prospective CS of 36 SSHL patients (Ullrich, 2004). 16/36 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 CR (Alpa, 2011) and a single CS (Luetje, 1997) using TPE in patients with SSHL have been published. In CR, TPE resulted in hearing recovery in ear not previously affected by SSHL. In CS, 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:
Replacement fluid: LDL apheresis: NA; Rheopheresis: NA; TPE: Albumin		1–2; TPE: 3 every other day

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.

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SYSTEMIC LUPUS ERYTHEMATOSUS

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

No. of reported patients: > 300	RCT	CT	CS	CR
Severe	1(20)	1(4)	14(128)	> 50
Nephritis	4(78)	2(114)	6(160)	16(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 (F:M 10:1) and African Americans present with more severe forms. Mortality of 70% at 10 years is due to infections and renal failure. Clinical symptoms are non-specific (fatigue, malaise, fever, anorexia, nausea, weight loss) and/or attributable to the involvement of one or more organ systems. SLE is an incurable chronic, remitting, and relapsing illness affecting any organ. Renal involvement (lupus nephritis) is associated with high mortality, but the extent and rate of progression is variable. Pathogenesis is more complex than simple deposition of DNA–antiDNA complexes, as recent observations site nucleosomes and possibly complement factor C1q as major factors. Nucleosomes serve as autoantigens and are presented to pathogenic T helper and B cells. Defect in apoptosis is also postulated to occur. Low complement levels and high titers of autoantibodies suggest active disease. Recent studies underscore potential role of T regulatory cells [CD4+CD25(high)FoxP3+], which are significantly decreased. Screening tests for antinuclear antibodies (ANA) are commonly positive which is confirmed through antibodies to double-stranded DNA (anti-dsDNA) and Sm antibodies.

Current management/treatment

Therapy entails immunosuppressive agents: cyclophosphamide, azathioprine, prednisone, methotrexate, cyclosporine, and mycophenolate mofetil. Newer agents target abnormal immune cells, including rituximab, epratuzumab, and anti-dsDNA tolerogen LJP394. Other experimental approaches include inhibition of the CD40–CD40 ligand pathway, inhibition of the B7 pathway, IL-10 blockade of, and anti-tumor necrosis factor therapy. Belimumab, fully human monoclonal antibody (B-lymphocyte stimulator (BlyS) inhibitor), was recently approved for SLE treatment other than lupus nephritis or neuropsychiatric lupus (Boyce, 2012). Hematopoietic stem cell transplantation is a salvage therapy inducing long-term immunologic remission (Marmont, 2012): one study reported 76% 5 year survival.

SLEDAI (SLE Disease Activity Index) and SLAM (SLE Activity Measure) are used to determine disease activity and therapy effeciacy. SLEDAI consists of 19 items (present or absent) representing nine organ systems. SLEDAI score > 5.0 defines active disease. SLAM includes 24 clinical manifestations for nine organ systems and eight laboratory variables, scored 0–2 or 0–3. Relationship between clinical impression and SLEDAI score has been recently evaluated: flare (increase in SLEDAI by > 3), improvement (reduction of SLEDAI by > 3), persistently active disease (change in SLEDAI $\pm \leq 3$), and remission (SLEDAI of 0).

Rationale for therapeutic apheresis

TPE was initially used 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 1980s it was reported that more than 50% of patients with various manifestations improved after TPE. However, the first RCT in mild SLE, where the patients underwent six 4L exchanges within 2 weeks with expected autoantibody and immune complex reductions, showed no clinical improvement (Wei, 1983). More recently, use of cyclosporine A 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, 2000). Multiple well-documented CRs of beneficial effect of TPE in SLE associated thrombotic thrombocytopenic purpura (TTP), diffuse aveolar hemorrhage (DAH), myasthenia gravis, hyperviscosity, and cryoglobulinemia have been published. A review of 26 patients with SLE and CNS involvement who were treated with TPE or TPE/cyclophosphamide revealed that 74% of patients improved, 13% stabilized, and 13% progressed (Neuwelt, 2003). These results highlighted potential benefit for refractory or critically ill patients.

A non-controlled trial of severe SLE patients ($n = 5$) undergoing TPE demonstrated that during the course of TPE (4–6 days) peripheral level of T-regs significantly increased, which was accompanied by decrease in SLEDAI, potentially due to the elimination of interferon alpha and lymphocytotoxic antibodies.

TPE in lupus nephritis is classified as Category IV as CT of TPE plus prednisone and cyclophosphamide versus prednisone and cyclophosphamide showed no TPE benefit (Lewis, 1992). Smaller later trials support these findings. A more recent RCT of severe lupus nephritis (Loo, 2010) suggested that adjunctive IA and TPE were equally effective in reducing SLEDAI scores. IA may be achieved with different high affinity columns and both TPE and IA remain as treatment strategies in patients with severe, refractory disease manifestations, and in pregnancy (Kronbichler, 2016).

Technical notes

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

Duration and discontinuation/number of procedures

Typically 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.

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THROMBOCYTOSIS

Incidence: ET: 0.01–2.61 per 100,000/yr; PV: 0.21–2.27 per 100,000/yr.	Indication	Procedure	Recommendation	Category
	Symptomatic	Thrombocytapheresis	Grade 2C	II
	Prophylactic or secondary	Thrombocytapheresis	Grade 2C	III
No. of reported patients: 100–300	**RCT**	**CT**	**CS**	**CR**
Symptomatic	0	0	7(180)	25(30)
Prophylactic or secondary	0	0	2(39)	3(4)

ET = essential thrombocythemia; PV = polycythemia vera

Description of the disease

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

ET is a clonal MPN characterized by autonomous overproduction of predominantly platelets. 80% of patients have mutations in *JAK2* mutation (JAK2V617F) ($\sim$55% of patients), calreticulin (*CALR*), or *MPL*. 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 (surgery or pregnancy). The cumulative rate of thromboembolism is 1.9–3% per patient per year. 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 bleeding risk. Studies support correlation between bleeding and platelet counts outside of the normal range (above or below), especially as extreme elevation in platelet count >1,500 $\times$ 10^9/L is associated with acquired von Willebrand syndrome (AVWS). Risk of hemorrhage also appears to be increased when 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 (>1000 $\times$ 10^9/L) in 5% of cases with postoperative thrombosis (10%) and bleeding (14%); however, platelet count does not predict thrombohemorrhagic complications.

Current management/treatment

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 extreme thrombocytosis if ristocetin cofactor activity is $\geq$30% (due to excess bleeding risk if <30%). In high-risk patients, platelet-normalizing therapy with hydroxyurea is indicated. Interferon-α or busulfan is used when poorly tolerant, or resistant to hydroxyurea. Platelet count should be normalized before surgery, particularly splenectomy, to minimize complications and avoid rebound thrombocytosis. Alternative platelet-lowering agents available include anagrelide, however, in high-risk ET patients this has been associated with increased risk of post-ET myelofibrosis. Interferon-α is the treatment of choice during pregnancy. Venous and arterial thromboembolic events are treated in accordance with national guidelines and institutional policy. Patients with extreme thrombocytosis and hemorrhage should be treated to lower the platelet count with medical therapy or thrombocytapheresis. Role of JAK-2 inhibitors in ET is currently undefined.

Rationale for therapeutic apheresis

Thrombocytapheresis has been utilized to prevent recurrent or treat acute thromboembolism or hemorrhage in selected patients with MPN and uncontrolled thrombocytosis. CRs 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 with PV or ET; although it is not indicated or beneficial for standard-risk pregnant women. Although the therapeutic mechanisms are not well defined, rapid cytoreduction is believed to ameliorate prothrombotic factors associated with the dysfunctional platelets. Restoring 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. 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, rationale is undefined and efficacy unproven.

Technical notes

Each procedure lowers the platelet count by 30–60%. Anticoagulant ratio of whole blood: anticoagulant should be 1:6–12; heparin should be avoided to prevent ex vivo platelet clumping.

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

Duration and discontinuation/number of procedures

With acute thrombohemorrhagic events, goal is normalization of platelet count and maintenance of normal count until cytoreductive therapy takes effect. Goal for prophylaxis of high-risk patients who are pregnant, undergoing surgery, or postsplenectomy should be determined on case-by-case basis (considering the patient's history of thrombosis or bleeding at a specific platelet count). Without an informative clinical history, platelet count of $\leq$600 $\times$ 10^9/L may be sufficient.

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THROMBOTIC MICROANGIOPATHY, COAGULATION MEDIATED

Incidence: Rare	Indication	Procedure	Recommendation	Category
	THBD mutation	TPE	Grade 2C	III
No. of reported patients: <50	RCT	CT	CS	CR
THBD mutation	0	0	1(6)	2(2)

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 etiologies for this syndrome are now classified. Atypical hemolytic uremic syndrome (aHUS) is now known to be mainly due to genetic mutations of complement and complement regulatory molecules leading to uncontrolled activation of the alternative complement pathway. This in turn, leads to TMA due to C3 tissue deposition, C5b-9 injury of endothelial cells, kidney injury, and hypertension. In the setting of aHUS investigations, scientists have learned that mutations in complement genes are not always present in those with disease and that some with mutations do not appear to have disease, suggesting incomplete penetrance and/or other genetic modifiers of function. Additionally, genetic mutations in proteins of the coagulation cascade appear to be implicated in the clinical syndrome of aHUS. This may be because underlying HUS pathophysiology is due to small vessel thrombosis; thus, genetic mutations of the coagulation proteins may increase the risk TMA.

Diacylglycerol kinase epsilon, DGKE, is a lipid kinase that catalyzed phosphorylation of arachinodonic acid containing phosphatidic acid to inhibit protein kinase C. Mutations may lead to pro-thrombotic state. Mutations in DGKE were found in up to 50% of children presenting with aHUS before 1 year of life. Thrombomodulin, THBD, is a thrombin cofactor that acts as an anticoagulant and also decreases CFI-induced inactivation of C3b. Six different mutations in the THBD gene have been found in seven unrelated patients that have clinical aHUS defined as ≥1 episode of TMA associated with renal failure and shiga toxin HUS was excluded. These mutations impair the function of thrombomodulin and thus may account for ∼5% of the underlying genetic mechanism in aHUS patients. The age range for affected patients with THBD mutations is 4–24 years, many with recurrent HUS episodes and some with normal C3 and C4 levels. Plasminogen, PLG, is a zymongen that is converted to plasmin, an antifibrinolytic serine protease that dissolves fibrin. In four patients with clinical aHUS, four different PLG mutations have been found that suggest plasminogen deficiency and deleterious protein function. Some patients had more than one deleterious genetic mutation. Other deleterious mutations found in aHUS patients include factor mutations (FXII, c1681-1G>A) and von Willebrand factor (c4165G>C and several others).

Current management/treatment

Initial management of coagulation protein gene mutation induced HUS/TMA may differ from other HUS management protocols. Because these genetic mutations are not all directly impactful on the complement cascade, therapy with eculizumab may not be beneficial. In fact, patients with DGKE mutations do not appear to benefit from eculizumab therapy, some having acute relapses while on the therapy. Renal transplantation may be efficacious in DGKA patients however, as relapses were not seen after transplant (in contrast to complement mediated aHUS patients). There are no publications on effective therapy in patients with THBD and PLG mutations.

Rationale for therapeutic apheresis

The benefit for TPE or plasma infusion is not consistent in these patient groupings. Further experience is needed to determine whether plasma can be a source for therapeutic intervention, although intuitively, plasma should contain the deficient coagulation factors absent or decreased in affected patients. The largest case series included six patients with THBD mutation that were part of a larger aHUS registry review. These six patients were treated for eight separate episodes, with remission achieved in seven episodes (88%) (five complete and two partial remissions). One patient died and one went on to ESRD. The authors suggest no difference in plasma infusion compared to TPE, although this includes all aHUS patients, not just THBD patients.

Technical notes

The specific TPE replacement fluid strategy and frequency are not described.

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

Duration and discontinuation/number of procedures

As there is no standardized approach, the duration and schedule of TPE for treatment has been empirically adopted in several patients, sometimes while diagnostic evaluation is ongoing.

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THROMBOTIC MICROANGIOPATHY, COMPLEMENT MEDIATED

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

No. of reported patients: 100–300	RCT	CT	CS	CR
Complement factor gene mutations	0	0	6(88)	N/A
Factor H autoantibody	0	0	4(115)	N/A

Description of the disease

New insights indicate that atypical hemolytic syndrome (aHUS) is caused by uncontrolled activation of the alternative complement system, now called complement-mediated thrombotic microangiopathy (TMA). It can manifest similar to HUS, but may have a chronic, progressive course, punctuated by catastrophic events such as acute kidney injury, retinal thrombosis, stroke, liver, and pancreatitis involvement, diarrhea, pulmonary hemorrhage, and peripheral thrombosis (Noris, 2009). Incomplete forms with mild or no typical hematologic features account for ~20% of cases. 40% occur in young adults.

A growing list of genetic mutations and polymorphisms are now known to predispose to complement-mediated TMA, primarily involving complement regulatory proteins, leading to complement-mediated endothelial injury. The primary event in the pathogenesis appears to be endothelial injury leading to formation of platelet-fibrin hyaline microthrombi which occlude arterioles and capillaries. Approximately 60% of cases involve 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%). 5% of cases are due to thrombomodulin mutations causing defective complement regulation (TMA-coagulation mediated factsheet). Acquired complement dysregulation has been reported in 6–10% due to anti-*CFH* autoantibodies (FHAA). Penetrance of genetic form is ~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. Disease may present with an insidious onset at any age but many cases present in 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 resulting from mutations in *CFHC* and *CFI*, C4 levels are normal but C3 levels are low due to functional C3 deficiency (both are normal in *MCP* mutations). In familial disease, lack of functional complement factors results in excessive activation of alternate complement pathway causing glomerular injury. Diagnosis relies on (1) lack of associated disease, (2) no criteria for Shiga-toxin HUS, i.e. negative stool culture and PCR for Shiga toxin, and (3) no criteria for TTP (ADAMTS13 activity >10%). Historically during the first year, 65% of all patients die, require dialysis, or have ESRD.

Current management/treatment

Empiric plasma therapy in all forms of complement-mediated TMA is still recommended, pending testing such as PCR for Shiga toxin, ADAMTS13, anti-CFH, and genetic testing. Once TTP, HUS, and drug or HSCT-TMA have been ruled out, the current recommended therapy is switching to eculizumab. Eculizumab, the humanized anti-C5 monoclonal antibody that blocks activation of the terminal complement cascade, has been shown to inhibit complement-mediated TMA and is effective in patients with and without identified genetic mutations. In contrast to TPE, the use Eculizumab not only can lead to recovery of hematological parameters, but can also lead to renal function recovery.

Rituximab and other immunosuppression may be initiated in combination with TPE in complement-mediated TMA due to FHAA. The data on the use of eculizumab in FHAA is limited albeit promising.

Kidney transplantation may be considered but risks recurrence of the disease process in the allograft; graft loss are common. The avaiblability of eculizumab may also reduce the need for kidney transplantation.

Rationale for therapeutic apheresis

The rationale for TPE use is that it can effectively remove the autoantibody or mutated circulating complement regulators while replacing absent or defective complement regulators. With the current understanding of the pathological mechanism and extensive use of eculizumab in this condition, use of TPE becomes somewhat limited. Before a firm diagnosis can be made, it is still considered as standard care to initiate TPE when TTP is suspected. When eculizumab is not available, TPE still remains an alternative treatment option, although the evidence suggests a more robust effect with eculizumab. For FHAA-related TMA, the combination of TPE and immunosuppression has been effective. TPE may not work for patients with MCP mutations, as the factor does not circulate and plasma therapy has in general not been shown to influence patient outcomes (Saland, 2009). However, there were two reports of the successful use of TPE in this setting.

Technical notes

Many affected patients 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	

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 complement-mediated TMA. Decisions of duration or to discontinue should be made based upon patient response and condition. When TPE is started before a firm diagnosis can be made, it is important to obtain and follow-up on the relevant laboratory testing such as PCR for Shiga toxin, ADAMTS13, anti-CFH as soon as possible, so approprte treatment pathway can be applied.

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THROMBOTIC MICROANGIOPATHY, DRUG-ASSOCIATED

Incidence: Clopidogrel/Ticlopidine: 0.001–0.0625%; CNIs: rare; Gemcitabine: 0.015–1.4%; Mitomycin: 2–15%; Quinine: rare	Indication	Procedure	Recommendation	Category
	Ticlopidine	TPE	Grade 2B	I
	Clopidogrel	TPE	Grade 2B	III
	CNIs	TPE	Grade 2C	III
	Gemcitabine	TPE	Grade 2C	IV
	Quinine	TPE	Grade 2C	IV
No. of reported patients: >300	RCT	CT	CS	CR
Ticlopidine/Clopidogrel	0	0	5(174)	7(7)
CNIs	0	0	7(94)	9(9)
Gemcitabine	0	0	3(39)	15(17)
Bevacizumab	0	0	1(6)	3(3)
Quinine	0	0	3(32)	8(8)

CNI = calcineurin inhibitors

Description of the disease

Recent review found that of 78 substances to have previously been reported to cause thrombotic microangiopathy (TMA), 22 had definite evidence supporting causal association. However, 9 (clopidogrel, cyclosporine, estrogen/progesterone, gemcitabine, interferon, mitomycin, quinine, tacrolimus, and ticlopidine) accounted for 76% of reports. TMA may result from an acute, immune-mediated reaction, presenting with the sudden onset of severe systemic symptoms, often associated with anuric acute kidney injury (AKI). An example is quinine-dependent antibodies directed at platelet glycoproteins, granulocytes, lymphocytes, and endothelial cells. TMA can also result from dose-dependent reactions which may be acute, caused by toxic dose of approved or illegal drug, or chronic, occurring after weeks or months of drug administration. Dose-dependent, toxicity-mediated TMA is also often associated with AKI. Many drugs including immunosuppressives, chemotherapeutics, and vascular endothelial growth factor (VEGF) inhibitors have been reported to cause TMA through dose- and time-dependent toxicity. With increase in sirolimus with calcineurin inhibitors (CNI) post HSCT there were reports suggesting an increased TMA incidence, however a recent meta-analysis did not support this association.

Current management/treatment

Initial management involves immediate discontinuation of suspected drug, or reduction of dose when discontinuation is not a medical option. Supportive care and other interventions reported for specific drugs include: Gemcitabine-dialysis, antihypertensives, corticosteroids, rituximab; Quinine-corticosteroids, antiplatelet agents; Bevacizumab-steroids, cyclophosphamide; Cyclosporine/Tacrolimus/Sirolimus—use alternative immunosuppression.

Rationale for therapeutic apheresis

TPE is based on extrapolation of its effectiveness for idiopathic TTP. However unlike idiopathic TTP, drug-associated TMA is rarely associated with severe deficiency of ADAMTS13 levels or presence of inhibitors. Pathogenesis is thought to be multifactorial including autoimmunity, drug-dependent antibodies, and endothelial toxicity. Other causative factors include presence and progression of pre-existing medical conditions such as malignancy, AKI, or hypertension. Therefore, therapeutic rationale for TPE is unclear, which is reflected in reported heterogeneous clinical results.

Thienopyridines: In Ticlopidine-associated TMA, ADAMTS13 levels are typically severely diminished (<10%) with inhibitors present (exception compared to other drug-associated TMA). Most patients develop TMA >2 weeks after initial drug exposure with majority of cases responding to TPE. With *clopidogrel*-associated TMA, ADAMTS13 levels are typically normal. Patients usually present ≤2 week of starting therapy. Most clopidogrel cases have mild hematologic and marked kidney involvement. The majority of rare cases of clopidogrel-associated TMA are unresponsive to TPE. This drug toxicity appears to occur by two different mechanistic pathways, characterized primarily by time of onset before versus after 2 weeks of thienopyridine administration. In patients developing TMA > 2 weeks after exposure TPE increased likelihood of survival (84% vs. 38%, $P < 0.05$). Among patients who developed TTP within 2 weeks of starting a thienopyridine survival was 77% with TPE and 78% without (Bennett, 2007). In a more recent case series with ticlopidine associated TMA, TPE was performed at a median of 3 days after onset of TMA (range 1–5 days), and TMA resolved at median of 8 days (range 3–28 days). Among four patients whose TMA cleared after 20 < days of TPE, ADAMTS13: INH titers were 2, 4·4, 17, and 20 BU/mL. Among 12 patients whose TMA resolved with TPE at <20 days, none had ADAMTS13: INH titers >4 BU/mL. Both ticlopidine-associated TMA deaths did not receive TPE. *CNIs*: TMA in these patients frequently do not have systemic manifestations. Response to TPE has been unpredictable even with extended TPE duration. In one CR with documented inhibitor to ADAMTS13 and depressed activity (17%), TPE was associated with improvement. *Gemcitabine*: ADAMTS13 levels are typically normal. In literature review, among 26 patients not treated with TPE, 56% recovered from TMA, whereas 30% of 18 patients who received TPE. However, the group receiving TPE appeared to be more severely ill and more likely to have received dialysis. *Bevacizumab*: ADAMTS13 levels are typically normal. One report described six treated cancer patients who developed TMA. One patient received five TPE, and kidney function stabilized. CR of TMA due to intravitreal ranizumab for macular degeneration has been reported. *Quinine*: ADAMTS13 levels are typically normal. TPE is relatively ineffective in the removal of quinine from the blood. There remains significant morbidity and mortality associated with TPE in quinine-associated TMA. In one controlled case series comparing quinine-TMA to nonquinine TTP-HUS in TPE treated patients, mortality was 21% vs. 41%, respectively, and development of ESRD was 57% vs. 16%. There is insufficient evidence to date to recommend any benefit from TPE for removal of quinine associated antibodies versus best supportive care.

Technical notes

Data regarding replacement fluid and frequency of TPE are limited. Similar procedural considerations apply as with TPE for TTP, however laboratory parameters and clinical response may be variable.

Volume treated: 1–1.5 TPV
Replacement fluid: Plasma

Frequency: Daily or every other day

Duration and discontinuation/number of procedures

Performed daily until recovery of hematologic parameters and then either discontinued or tapered off, similar to treatment for idiopathic TTP.

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THROMBOTIC MICROANGIOPATHY, HEMATOPOIETIC STEM CELL TRANSPLANTATION ASSOCIATED

Incidence: 1-yr cumulative 13% (non-myeloablative) and 15% (myeloablative)		Procedure TPE	Recommendation Grade 2C	Category III
No. of reported patients: >300	RCT 0	CT 0	CS 24(355)	CR 7(8)

Description of the disease

Thrombotic microangiopathy (TMA) following allogeneic hematopoietic stem cell transplantation (HSCT, also called bone marrow transplant associated [BMT]-TMA) appears to be primarily triggered by mechanisms of endothelial cell injury, including high-dose conditioning chemotherapy, irradiation, graft-versus-host disease (GVHD), mTOR, and calcineurin inhibitor drugs (used to prevent and treat GVHD) and infections. Damaged and apoptotic endothelial cells generate inflammatory cytokines, microparticles, release of von Willebrand factor (vWF), and induce platelet adhesion/aggregation and a procoagulant state. In contrast to idiopathic thrombotic thrombocytopenic purpura (TTP), plasma ADAMTS13 protease level is not severely deficient nor is ADAMTS13 inhibitor activity detectable. In addition, a recent study suggests the involvement of complement dysregulation.

The incidence varies based on the diagnostic criteria and transplant-associated risk factors. Incidence rates in older studies ranged from 0.5 to 63.6%; however, rates in more recent studies range from 3 to 15% with a prevalence of 10–25%. Kidneys are the major target organs of HSCT-TMA. Renal dysfunction is common and renal failure is a poor prognostic feature. Diagnostic criteria vary but require microangiopathic hemolytic anemia (MAHA; with high LDH and low haptoglobin) with or without unexplained thrombocytopenia, renal, and/or neurologic dysfunction. Because MAHA can be due to other causes and drugs, published criteria for HSCT-TMA diagnosis are relatively insensitive. HSCT-TMA can occur within first few weeks following transplant or as a late complication (up to 8 months). HSCT-TMA carries a poor prognosis. Mortality rates range from 44 to 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 HSCT-TMA involves reduction or discontinuation of mTOR and calcineurin inhibitor drugs (especially if used in combination), if applicable, along with aggressive treatment of underlying GVHD and infections. Other treatment options include rituximab, defibrotide, vincristine, pravastatin, eculizumab, and TPE. No RCTs have addressed the efficacy of TPE for HSCT-TMA. CSs have reported overall response rates with TPE (usually after drug withdrawal) ranging from 0 to 72%, but with frequent partial responses, relapses and up to 15% procedural adverse events. One study of 63 patients observed TPE responses only among those who also responded to treatment of GVHD and/or infections, suggesting that TPE alone does not reverse the TMA pathophysiology. A systematic review (George, 2004) of published 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 HSCT-TMA. Because some patients appear to respond to TPE, a trial TPE could be considered as salvage therapy for selected patients with persistent/progressive HSCT-TMA despite resolution of infections and GVHD. A recent retrospective review performed in 10 pediatric patients with TA-TMA suggests that early initiation of TPE might be beneficial even in patients with multiorgan failure.

Rationale for therapeutic apheresis

The use of TPE 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, therapeutic rationale is undefined and consistent with the uncertain clinical efficacy.

Technical notes

TPE for patients with HSCT-TMA is often complicated by thrombocytopenia, anemia, and co-morbidities related to GVHD and infections, including bleeding and hypotension. Therefore, 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	

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. TPE has also been performed with alternative schedule such as initially daily, then every other day for ∼2 weeks, then twice a week.

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.

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THROMBOTIC MICROANGIOPATHY, SHIGA TOXIN MEDIATED

Incidence: STEC-HUS: 0.5–2/100,000 in general population; pHUS following invasive S. pneumoniae infection: 0.4–0.6%	Indication	Procedure	Recommendation	Category
	Severe neurological symptoms	TPE/IA	Grade 2C	III
	pHUS	TPE	Grade 2C	III
	Absense of severe neurologic symptoms	TPE	Grade 1C	IV

No. of reported patients: >300	RCT	CT	CS	CR
STEC	1(35)	1(37)	56(1,403)	103(118)
pHUS	0	0	2(12)	3(3)

STEC-HUS = thrombotic microangiopathy, Shiga toxin-mediated. pHUS = thrombotic microangiopathy *Streptococcus pneumonia*.

Description of disease

One of the most common thrombotic microangiopathies (TMAs), hemolytic uremic syndrome (HUS), is a potentially life-threatening condition characterized by TMA that typically targets the kidney causing renal failure. In the majority (90%) of patients with HUS, the cause is due to the action of Shiga-like toxin (Stx) on the renovascular endothelium and is often referred to as STEC-HUS (D+HUS). STEC-HUS occurs most frequently in younger children, and 2–10 days after a prodrome of bloody diarrhea due to verocytotoxin (Stx)-producing bacteria, predominantly *E. coli* O157:H7. Outbreaks and sporadic cases linked to other *E. coli* serotypes, *Shigella dysenteriae*, or other microorganisms producing Stx continue to be reported. In most series, STEC enteritis usually leads to HUS in 5–15% of cases. In 2011, Europe experienced one of the largest recorded STEC-HUS outbreaks. A total of 3,842 people were affected by a virulent and uncommon strain of *E. coli*: enteroaggregative hemorrhagic *E. coli* (EAHEC) O104:H4. HUS developed in 855 (80% adults) with 54 deaths reported. Stx have proinflammatory and prothrombotic effects on the vascular endothelium and may attach to and stimulate endothelial cells to release "unusually large" von Willebrand factor multimers (UL VFWM) 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 vascular endothelial cell damage, thrombotic occlusion of the capillary lumen, glomerular endothelial cell swelling, apoptosis of glomerular and tubular cell, and extensive cortical necrosis in the kidneys. About a third of cases will require dialysis. Recurrent kidney injury may occur. Brain endothelial and neuronal cells are also targeted. The severity of acute illness, particularly central nervous system impairment and the need for dialysis is strongly associated with a worse long-term prognosis. Mortality is between 1 and 5% but up to 30% of patients may have long-term complications including, hypertension, ESRD requiring renal transplantation, diabetes, and neurological symptoms.

Another infection-induced HUS that usually occurs in children <2 years is due to sepsis, pneumonia, or meningitis caused by *Streptococcus 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. Mortality rates are as high as 50%.

Current management/treatment

Supportive care is the mainstay of therapy including fluid management, treatment of hypertension and renal replacement therapy. There is no evidence of any benefit of glucocorticoid therapy. There is no compelling evidence from the available literature that TPE benefits patients with STEC-HUS, although patients with severe bloody diarrhea or neurological involvement may respond to timely TPE. In the 2011 outbreak in Germany (Menne, 2012), TPE was carried out in 251 patients yet evidence of benefit was not seen. However, in the same outbreak, TPE appeared to ameliorate the course in five adults, with AKI and CNS dysfunction, treated in Denmark (Colic, 2011). In the same 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, 2011). Previously a retrospective study from France had identified acute neurological involvement in STEC-HUS, half of whom responded to TPE (Nathanson, 2010) suggesting some benefit in this specific clinical setting.

Stx has been shown in vitro and in vivo to activate the alternative complement pathway. In the 2011 outbreak of STEC-HUS, the use of eculizumab demonstrated no significant difference in outcome compared to patients treated with TPE (Menne, 2012). Similarly in the same outbreak, a French group found no difference in patient outcome with the use of eculizumab however suggested that as potentially more severely ill patients were treated with eculizumab, and that they still showed a comparable outcome compared to untreated patients, this may point toward an advantageous use, at least for severe cases (Delmas, 2014).

Rationale for therapeutic apheresis

TPE may reduce concentrations of various cytokines, UL VWFM, and Stx that damage the endothelium however there is limited data to support this. Free Stx has not been detected in the serum, and how it transits from the GI tract to target organs remains unclear. For pHUS, TPE would remove antibodies directed against the exposed T-antigen, as well as circulating bacterial neuraminidase. Experience with TPE for pHUS is limited without reported adverse effects.

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.

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

Duration and discontinuation/number of procedures

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.

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THROMBOTIC THROMBOCYTOPENIC PURPURA

Incidence: 0.37/100,000/yr (US)		Procedure	Recommendation	Category
		TPE	Grade 1A	I
No. of reported patients: > 300	RCT	CT	CS	CR
	7(301)	2(133)	38(1541)	N/A

Description of the disease

Thrombotic thrombocytopenic purpura (TTP), also known as TMA-ADAMTS13 deficiency, is a systemic thrombotic illness affecting mostly small vessels. Originally defined by the pentad of thrombocytopenia, microangiopathic hemolytic anemia (MAHA), mental status changes, renal failure, and fever, currently, clinical findings of unexplained thrombocytopenia and MAHA are sufficient to diagnose TTP. Because TTP is potentially fatal if left untreated, there should be a low threshold to treat presumed TTP. Treatment is usually initiated urgently within 4–8 h of diagnostic suspicion, after other causes of systemic TMA such as disseminated intravascular coagulopathy, severe malignant hypertension, pernicious anemia (vitamin B12 deficiency), HUS, and post-transplant TMA have been considered unlikely and working clinical diagnosis of TTP is made. TTP is associated with a severe (<10%) deficiency of plasma ADAMTS13 enzyme activity, which is responsible for maintaining normal distribution of VWF multimers. Severe ADAMTS13 deficiency becomes a corner stone for making a diagnosis of TTP; however lacking so does not exclude TTP. Congenital TTP is associated with somatic mutations resulting in severely deficient ADAMTS13 function. Autoantibody presence 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 disease recurrence. Pregnancy, connective tissue disease, medications, infection, cancer, and transplantation are associated with TTP, HUS, and TMA syndromes. Diagnostic criteria to differentiate TTP from different types of HUS (characterized by TMA, thrombocytopenia, and renal failure) are still evolving.

Current management/treatment

TPE has decreased overall mortality of idiopathic TTP from nearly 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. Corticosteroids are often used as an adjunct at 1 mg/kg/day; however, no definitive trials proving 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 adjunctive agent with initial TPE. Since rituximab immediately binds to CD20-bearing lymphocytes, a 18–24 h interval between its infusion and TPE is 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 only be transfused for significant clinical indications such as potential life-threatening bleeding. 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 von Willebrand factor concentrates (used to treat von Willebrand disease) have been used. Most recently the use of anti–von Willebrand antigen antibody is being evaluated.

Rationale for therapeutic apheresis

TPE with plasma replacement has significantly improved patients' clinical outcomes. One hypothesis is that TPE removes anti-ADAMTS13 autoantibody, while replacing ADAMTS 13 protease activity. However, clinical course does not always correlate with plasma ADAMTS13 activity or ADAMTS13 inhibitor levels.

Technical notes

Transfusion of RBC, when medically necessary, may be given emergently around the time of apheresis. 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 whole blood) to minimize citrate reactions, especially for patients with moderate to severe thrombocytopenia. Fibrinogen levels may decrease following serial TPE procedures with cryoprecipitate poor plasma as replacement. One recent study showed that the use of cryoprecipitate poor plasma as replacement may be associated with more frequent acute exacerbations. In patients with severe allergic reactions to plasma proteins or limited supply of ABO compatible plasma, 5% albumin may be substituted for the initial portion (up to 50%) of replacement. Solvent detergent treated plasma may be used for patients with severe allergic reactions. In addition, combined use of 50% albumin and 50% plasma has been reported to result in similar treatment efficacy as compared to the replacement of 100% plasma (O'brien, 2013). Albumin alone without any plasma replacement or infusion however has never shown efficacy.

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

Duration and discontinuation/number of procedures

TPE is generally performed daily until the platelet count is $>150 \times 10^9$/L, and LDH is near normal for 2–3 consecutive days. 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.

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THYROID STORM

Prevalence: 1/100,00 (about 1% of individuals with thyrotoxicosis)		Procedure TPE	Recommendation Grade 2C	Category III
No. of reported patients:< 100	**RCT** 0	**CT** 0	**CS** 4(23)	**CR** 20(25)

Description of the disease

Thyroid storm, thyrotoxic storm, or accelerated hyperthyroidism is an extreme manifestation of thyrotoxicosis. This uncommon but serious complication occurs mostly in Graves' disease and less often in toxic multinodular goiter. Symptoms are usually, not always, precipitated by infection, trauma, surgical emergencies, withdrawal of anti-thyroid medications, operations (particularly thyroidectomy), radiation thyroiditis, diabetic ketoacidosis, severe emotional stress, cerebrovascular disease, use of tyrosine-kinase inhibitors, toxemia of pregnancy, or parturition. Amiodarone-induced thyroid storm is more prevalent in iodine-deficient geographic areas. Crises are usually sudden in patients with pre-existing hyperthyroidism that had been partially or untreated. Burch and Wartofsky created a scoring system to help standardize its diagnosis using body temperature, central nervous system involvement, gastrointestinal-hepatic dysfunction, heart rate, and presence or absence of congestive heart failure and/or atrial fibrillation. The clinical picture is one of severe hypermetabolism: fever (may be $> 40°C$), marked tachycardia and arrhythmias, potentially with pulmonary edema or congestive heart failure, tremulousness and restlessness, delirium or frank psychosis, nausea, vomiting, abdominal pain, and, as the disorder progresses, apathy, stupor, and coma, and hypotension. This clinical picture in a patient with a history of pre-existing thyrotoxicosis, with goiter or exophthalmos, is sufficient to establish the diagnosis, and emergency treatment should not await laboratory confirmation. There is no serum T_3 or T_4 concentration that discriminates between severe thyrotoxicosis and thyroid storm. If unrecognized, the condition may be fatal; mortality is 10–30% even with treatment. The most agreed upon pathogenesis is the presence of both larger availability of adrenergic receptors and a reduction of thyroid hormone binding to thyroid hormone binding globulin (TBG) result in leaking catecholamines to precipitate thyroid storm.

Current management/treatment

American Association of Clinical Endocrinologist recommends a multimodality treatment approach. Their management includes medications which stop the synthesis (propylthiouracil or methimazole), release (iodine), blocking T_4 to T_3 conversion (dexamethasone), enhancing hormone clearance (cholestyramine), peripheral effects of the thyroid hormones (beta-blockers such as propranolol), manages high fever (acetaminophen, cooling blankets), and hypotension (hydrocortisone). If a precipitating event is present, it should also be treated concurrently. The order of treatment is important. Propylthiouracil (PTU; 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 clinical status, the two agents may be administered as close as 30–60 min apart. Large doses of antithyroid agent (500–1000 mg loading dose of propylthiouracil followed by 250 mg every 4 h and 60–80 mg per day of methmazole in divided doses) are given orally, by stomach tube, or per rectum. PTU is preferable to methimazole because it has the additional action of inhibiting generation of T_3 from T_4 in peripheral tissues and thyroid. Controlling the cardiovascular manifestations of thyroid storm is vital. Relatively large doses (60–80 mg every 4 h) 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. Aspirin or other salicylates should not be used because they increase serum hormone levels.

Rationale for therapeutic apheresis

TPE is reserved for patients with thyroid storm with severe symptoms and first-line therapies discussed above fail or cannot be used due to toxicity, such as leukopenia due to PTU. 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 T_4 serum level, suggesting earlier TPE is more efficient. In patients with amiodarone-associated thyrotoxicosis, TPE has also been used to reduce the amiodarone plasma concentration, 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 result from removal of 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 thyrotoxocotic patient euthyroid prior to thyroidectomy. TPE effect is transient and hormone levels typically rise again the next day. A case using continuous veno-venous hemodialysis with a dialysate containing 4% human serum albumin was reported to improve symptoms and remove more thyroid hormone than TPE.

Technical notes

Plasma as replacement fluid has the advantage of increasing the concentration of TBG to bind free thyroid hormone. However, albumin provides a larger capacity for low-affinity binding of thyroid hormones.

Volume treated: 1–1.5 TPV	**Frequency**: Daily to every 3 days
Replacement fluid: Plasma, albumin	

Duration and discontinuation/number of procedures

TPE should be continued until clinical improvement is noted.

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TOXIC EPIDERMAL NECROLYSIS

Incidence: 2/1,000,000/yr	Indication	Procedure	Recommendation	Category
	Refractory	TPE	Grade 2B	III
No. of reported patients: 100–300	**RCT**	**CT**	**CS**	**CR**
	0	0	11(126)	9(11)

Description of the disease

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), also called Lyell syndrome, represent a spectrum of severe idiosyncratic reactions with medications being the most common trigger. They are characterized by mucocutaneous lesions leading to necrosis and sloughing of the epidermis. 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, starting on the face and chest before spreading to other areas. Vesicles and bullae form followed, usually within days, by skin sloughing. Prognosis is related to the extent of epidermal involvement. Re-epithelialization typically occurs with 1–3 weeks. Fulminant cases of TEN highly resistant to therapy have been described. Skin biopsy in TEN shows full thickness epidermal necrosis, subepidermal detachment, and mild lymphocytic infiltration at the dermoepidermal junction. Mortality in SJS is 1–3%, while mortality for TEN is 25–30%. The pathogenesis of SJS/TEN remains incompletely understood. 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. There is a strong association between the HLA-B*1502 allele and carbamazepine induced TEN.

Current management/treatment

For medication-induced SJS/TEN, the causative mediation 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 1 and 3 of hospitalization for TEN. Supportive care, typically in an intensive care unit or burn center, is the mainstay of treatment and includes skin care, fluid and electrolyte management, nutritional support, eye care, temperature management, appropriate analgesia, and treatment of infections (Seczynska, 2013). 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. Aggressive culturing and sterile precautions are important in minimizing this risk. Use of prophylactic antibiotics is not recommended. Beyond supportive care, there are no universally accepted therapies for this disease. The effectiveness of glucocorticoids, cyclosporine, IVIG, TPE, biologics, and other agents remains uncertain.

Rationale for therapeutic apheresis

The rational supporting TPE in TEN includes removal of drug/drug metabolites, cytokines, or other mediators of keratinocyte cytotoxicity. One case series has demonstrated decreased levels of serum cytokines following TPE (Narita, 2011). TPE is typically not used in patients with SJS although there is a recent CR of TPE use for SJS complicated by hepatic encephalopathy (Hung, 2014).

Numerous CSs have utilized TPE in the setting of severe cases of TEN refractory to standard treatment. Most have suggested that TPE is efficacious, however, one CS of eight patients showed no difference from supportive care (Furubacke, 1999). Given the 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. Recently published CRs describe application of TPE in combination with other therapies (White, 2014; Balint, 2014).

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 TPV   **Frequency**: Daily or every other day
Replacement fluid: Plasma, albumin

Duration and discontinuation/number of procedures

The number of TPE treatments varies considerably from 1 to >5 procedures. Discontinuation has been guided by clinical improvement including pain relief, the lack of appearance of new skin lesions, or evidence of skin healing.

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VASCULITIS

Incidence: PAN: <5–77/1,000,000; EGPA: 2–13/1,000,000	Indication	Procedure	Recommendation	Category
	HBV-PAN	TPE	Grade 2C	II
	Idiopathic PAN	TPE	Grade 1B	IV
	EGPA	TPE	Grade 1B	III
	Behcet's disease	Adsorption granulocytapheresis	Grade 1C	II
	Behcet's disease	TPE	Grade 2C	III

No. of reported patients: >300	RCT	CT	CS	CR
PAN/EGPA	2(140)	1(342)	2(76)	NA
HBV-PAN	0	0	1(115)	NA
Behcet's disease/TPE	0	0	1(4)	3(3)
Behcet's disease/Adsorption granulocytapheresis	0	0	2(18)	2(3)

PAN = polyarteritis nodasa; HBV = hepatitis B; EGPA = eosinophilic granulomatosis with polyangiitis.

Description of the disease

Vasculitis involves inflammation in blood vessels including arteries, veins, and capillaries. There are many types of vasculitis. Poly-arteritis nodosa (PAN) is a form of vasculitis that mainly affects medium-sized arteries, frequently presenting with peripheral neuropathy, skin, renal, and other organ and system manifestations, some of these are non-specific: weight loss, fever, myalgia, rash, neuropathy, or abdominal ischemia. It typically spares pulmonary and glomerular arteries. It may also involve single organ or skin only. PAN is not associated with anti-neutrophil cytoplasmic antibodies (ANCA). It can be idiopathic, or associated with infection such as hepatitis B virus (HBV). People between 40 and 60 years are most often affected. There is no specific test to diagnose PAN.

Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg Strauss Syndrome) is one of the ANCA-associated vasculitis. EGPA is a rare vasculitis of small- and medium-sized vessels. It is almost always associated with asthma and eosinophilia, and in ~40% of the patients, anti-myeloperoxidase (MPO) anti-neutrophil cytoplasmic antibodies (ANCA) is detected. It can involve the peripheral nerves and skin, but can be seen in other organs such as the heart, kidney, and gastrointestinal tract. Patients with anti-MPO ANCAs are more likely to suffer more severe vasculitis symptoms, such as glomerulonephritis, mononeuritis multiplex, and alveolar hemorrhage, than ANCA-negative patients. People >50 years are most often affected.

Behçet's disease (BD) is a rare immune-mediated systemic vasculitis that can involve blood vessels of all sizes and can affect both the arterial and venous vessels. It is a chronic relapsing-remitting immuno-inflammatory disorder with a variety of clinical manifestations including orogenital ulceration, ocular, vascular, central nervous system, articular, mucocutaneous, and gastrointestinal symptoms. It is found primarily in Asia and with high prevalent in HLA B51 individual. Most manifestations are self-limiting, but repeated attacks of uveitis are a major cause of blindness.

Current management/treatment

For HBV-PAN, treatment includes glucocorticoids, anti-viral medications, and TPE. Because of the effective HBV vaccination, HBV-PAN is uncommonly seen. For idiopathic PAN, treatment consists of glucocorticoids and immunosuppression such as cyclo-phosphamide. Mainstay of therapy for EGPA is glucocorticoids. In addition, immunosuppressions such as cyclophosphamide have been used for patients with severe disease manifestations. More than 90% of patients can be managed with steroid initially and achieve remission. The Five-Factor Score (FFS) has been used for PAN and EGPA for evaluating disease severity and prognosis. Patient with renal symptoms, gastrointestinal tract involvement, cardiomyopathy, central nervous system involvement, loss > 10% of body weight, and age > 50 years may have poor prognosis and require maintenance treatment. Current management of BD includes topical medication, systemic steroids, antibiotics, and immunosuppressive and anti-inflammatory agents. TPE and granulocyte and monocyte adsorption apheresis have also been tried with some success.

Rationale for therapeutic apheresis

Pathogenesis of HBV-PAN has been attributed to immune-complexes which may be removed by TPE. The combination of TPE, steroids, and antiviral agent has been shown to be effective in several CSs for HBV-PAN. In one CS (Guillevin, 2005), 115 patients received TPE and immunosuppression, some also received anti-viral medication. At a mean follow-up of 69 months, 93 (80.9%) patients were in remission, 22 (19.1%) did not achieve remission and had died.

Several RCT have not shown any additional benefit of TPE to corticosteroids in reducing relapse rates for idiopathic PAN and EGPA. A RCT (Guillevin, 1992) performed in 78 patients with PNA (60, excluding HBV-PAN) and EGPA (18) demonstrated that the prednisone and TPE combination was no more effective than corticosteroids alone in preventing relapses over the long-term. Similarly, TPE has not been shown to be beneficial in patients with glomerulonephritis in PAN or EGPA. However, according to the Eosinophilic Granulomatosis with Polyangiitis (Churg–Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management, TPE can be considered for selected patients with ANCA and RPGN or pulmonary–renal syndrome.

TPE may remove immune complexes in BD. Adsorption granulocytapheresis may remove NK cells or other cells that are implicated in the inflammational response in BD. In one study (Namba, 2006), 9 out of 14 (64%) patients with refractory ocular BD who underwent granulocytapheresis showed improvement, and patients who had a long duration of disease are better responders.

Technical notes

Volume treated: 1 TPV	**Frequency**: See below
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

For HBV-PAN, 9–12 TPEs (over 2–3 per week) had been used. For ocular BD, five granulocytapheresis sessions performed at one session/week over five consecutive weeks have been used.

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VOLTAGE-GATED POTASSIUM CHANNEL ANTIBODIES

Incidence: Rare		Procedure	Recommendation	Category
		TPE	Grade 2C	II
No. of reported patients: < 100	RCT	CT	CS	CR
	0	0	6(31)	27(29)

Description of the disease

Voltage-gated potassium channels (VGKCs) are membrane proteins that 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 wide range of cells, but are most important in the control of membrane excitability in the nervous system. VGKC complex antibodies were initially described in adults with limbic encephalitis (LE). Recently, other proteins tightly complexed with the potassium channel were described as the target antigens for VGKC antibodies, including leucine-rich, glioma inactivated 1 (LGI1), Contactin-associated protein-2 (CASPR2), and contactin-2. Additional specificities remain undefined. Most adults who tested positive for VGKC autoantibodies were positive for antibodies to one or more of those antigens.

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 and more rarely (<20%) in some patients with neoplastic conditions. Three neurological conditions have been strongly associated with the presence of VGKCs autoantibodies: 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 tends to occur in the 5th decade for NMT and 6th/7th decade of life in LE. Morvan's syndrome presents with autonomic dysfunction in addition to the symptoms seen in LE and NMT. Overall, 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 the order of months to years). In addition, association with neoplastic disease in some patients complicates evaluation and final diagnosis. Since the discovery of VGKC antibodies, some conditions, previously considered only for empirical treatment, have received better explanation of pathogenesis based on interaction of the autoantibody with the VGKC receptor on cell membranes in the central and peripheral nervous system. Thus, different immunotherapies have been used in LE, NMT, and MVS, including steroids, IVIG, TPE, cyclosporine, mycophenolate mofetil, and rituximab in addition to symptomatic treatment (e.g., anti-seizure medication). Acute therapy usually consists of steroids and/or IVIG. TPE is typically added if patient is unresponsive to steroids/IVIG. Of note, most recent series have reported that early diagnosis and initiation of immunomodulation therapy have led to better control of symptoms such as seizure, which are often resistant to conventional anti-seizure medications.

Rationale for therapeutic apheresis

There is a clear rationale for the use of TPE in the autoimmune condition. Multiple case reports showed that VGKC antibodies decrease with TPE, and this is associated with clinical improvement. Wong (2010) reported in an open label prospective study immunotherapy protocol consisting of IV methylprednisolone (1 g/day for 3 days), TPE of 5 treatments over 7–10 days typically after completion of IV methylprednisolone (but occasionally used concurrently), followed by IVIG (2 g/kg over 5 days) and maintenance therapy with oral prednisolone (1 mg/kg). Using this regimen on nine 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, normalization of changes on MRI, and significantly decreased VGKC antibody levels. Vincent (2004) reported on a two-center retrospective analysis of 10 patients with LE. TPE was administered in seven patients in conjunction with steroids and IVIG. Four of seven patients reported complete resolution and 2 of 7 reported slight improvement. It was noted that early steroid administration was associated with faster decrease in antibody titers. Jaben (2012) reported on five retrospectively identified patients with neurological symptoms and VGKC antibodies treated with TPE. There was a durable clinical response in three of these patients. These data suggest that there is beneficial and, possibly, synergistic effect of TPE and steroids in the setting of these neurological conditions. Moreover, in some of the reports, TPE was used as a chronic therapy to maintain low antibody levels and to control symptoms. The frequency of maintenance TPE varied from a limited course of 10 TPEs over 5 weeks to open-ended treatment ranging from 1 TPE/every 3 weeks to every 3 months.

Technical notes

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 typically used. Anti-VGKC titers often correlate with symptoms' severity. Thus, serial measurements of those titers are often performed after the series of treatments to monitor disease activity and evaluate response.

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As of July 6, 2015, 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.

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WILSON'S DISEASE, FULMIMANT

Incidence: Rare		Procedure TPE	Recommendation Grade 1C	Category I
No. of reported patients: < 100	RCT 0	CT 0	CS 2(6)	CR 22(23)

Description of the disease

Wilson's disease is an autosomal recessive genetic disorder resulting from a mutation in the *ATP7B*, which encodes a copper transporting ATPase protein, leading to impaired biliary copper excretion, resulting in copper accumulation in the liver, brain, cornea, and kidney. Copper's incorporation into ceruloplasmin is also impaired. Birth incidence rates are 1/30,000–40,000. It has been estimated that ~1% of the population are carriers. The disease usually presents between ages 5 and 35 years. Children present with asymotomatic liver deposits of copper, teenagers with liver disease, and adults with neurological symptoms. The spectrum of liver disease includes asymptomatic liver function test (LFT) abnormalities, hepatitis, cirrhosis, and acute liver failure (ALF). Neurological symptoms include Parkinsonism, dystonia, cerebellar, and pyramidal symptoms. History of behavioral disturbances is present in half of patients with neurological disease. The appearance of Kayser–Fleischer rings (copper deposits in the outer rim of the cornea) and direct antiglobulin test negative hemolytic anemia are relatively common. The hemolysis appears to be primarily due to copper-induced oxidant stress to RBC enzyme pathways and membrane damage. ALF is typically accompanied by hemolytic crisis and multiorgan failure with rapid clinical deterioration, and is nearly always fatal without liver transplantation (LT). No laboratory test is diagnostic but suggestive results include low serum ceruloplasmin, increased 24-h urinary copper excretion, and elevated serum copper. The gold standard for diagnosis is a liver biopsy showing elevated copper content. A genetic test for *ATP7B* is available.

Current management/treatment

Asymptomatic patients should be treated, since the disease is almost 100% penetrant. Low-copper diets are recommended. Zinc acetate is nontoxic and stimulates metallothioneine which reduces dietary and enterohepatic absorption of copper. It is the therapy of choice for asymptomatic patients or patients with hepatitis or cirrhosis, but without evidence of hepatic decompensation or neurologic/psychiatric symptoms. Zinc is also first choice in pediatric and pregnant patients. Chelation therapy (penicillamine, trientine) increases urinary copper excretion. Trientine has replaced penicillamine as the primary chelator due to less toxicity. If penicillamine is given, it should always be accompanied pyridoxine (25 mg/day). Chelation can be used as a temporizing agent to treat the enormous release of copper into the blood stream in ALF 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 including hemofiltration, albumin dialysis, and the Molecular Adsorbents Recirculating System (MARS). For initial neurologic therapy, tetrathiomolybdate is emerging as the drug of choice because of its rapid action, preservation of neurologic function, and low toxicity. Anticopper therapy must be life-long. LT is potentially curative and is the main stay of therapy for patients with ALF. Disease severity is estimated using a prognostic score which is based on a combination of laboratory values, most commonly LFTs and coagulation status (INR/PT). LT reverses most of the clinical and biochemical pathological manifestations of the disease within few months.

Rationale for therapeutic apheresis

Donor organs for LT are not always available and temporizing treatments must be aimed at treating the release of massive amounts of copper into circulation. In this scenario, TPE can be beneficial as it rapidly remove significant amount of copper from the circulation—average of 20 mg per TPE treatment. Decreased serum copper may decrease hemolysis, prevent progression of renal failure, and provide clinical stabilization. TPE can also remove large molecular weight toxins (aromatic amino acids, ammonia, endotoxins) and other factors which may be responsible for hepatic coma. In most reported cases, TPE was used as a bridge to LT. Interestingly, recent reports showed that TPE combined with chelating agents improved ALF and eliminated need for LT. In addition, the widespread availability of TPE over MARS or equivalent technology makes it a more accessible reasonable choice of therapy.

Technical notes

Plasma replacement rapidly corrects coagulopathy. Plasma/albumin combination is also possible as 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

Serum copper reduction in most CRs had been achieved rapidly and maintained after the first two treatments. However, the total number of TPE performed is variable (1–11), depending on LT availability or recovery. 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 is based on clinical parameters and routine testing (i.e., improved encephalopathy and LFTs & controlled hemolysis).

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