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

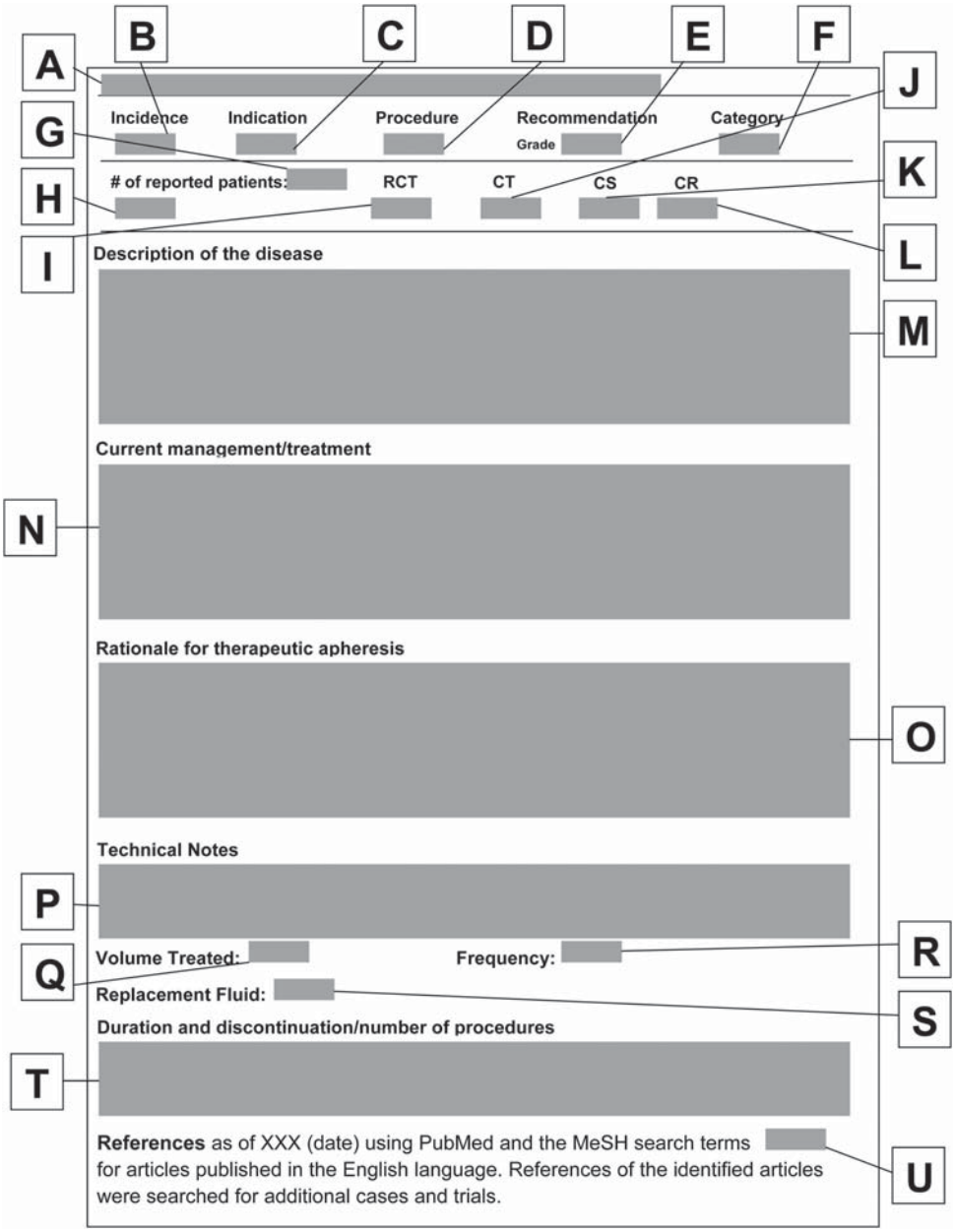

Fig. 1. Explanation of the fact sheet used in the ASFA Special Issue, Seventh Edition (2016).

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

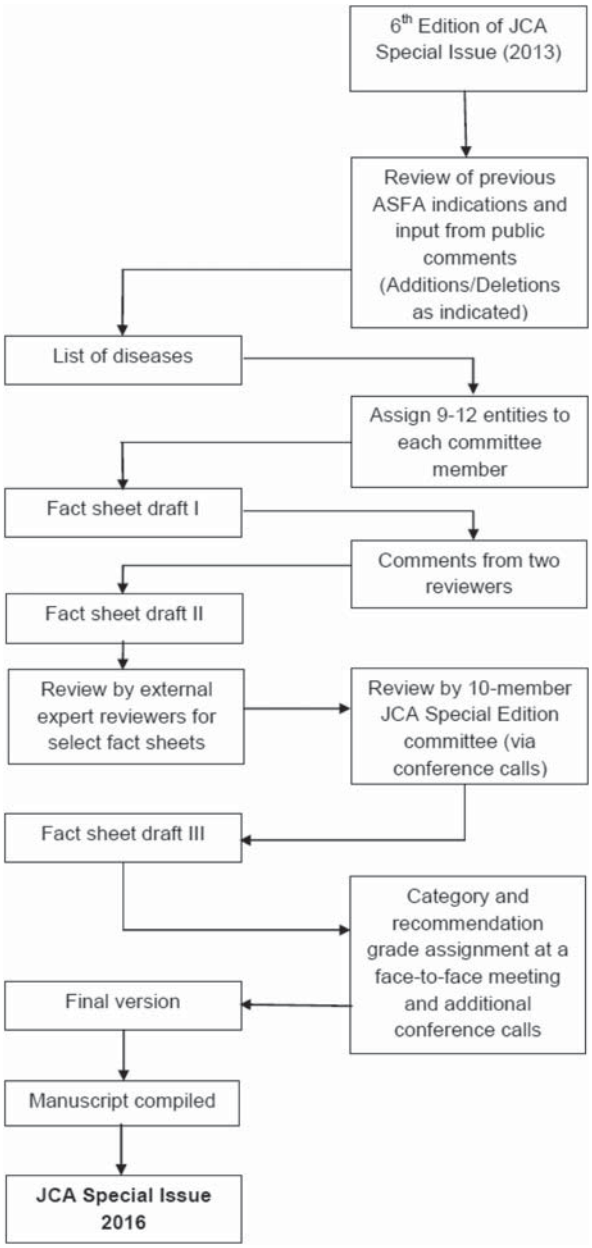

Fig. 2. Systematic approach to ASFA category and recommendation grade assignment, fact sheet generation, and revision in the JCA Special Issue 2016.

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

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 allloimmunization 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

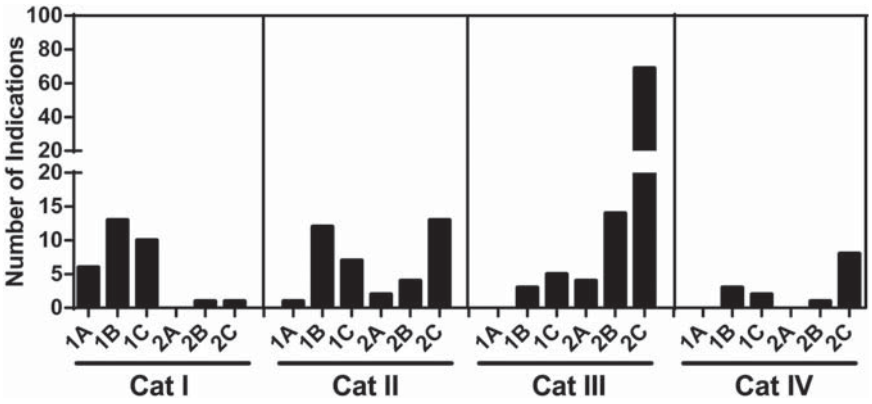

Fig. 3. The ASFA category indications and the recommendation grade in the JCA Special Issue 2016.

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, α2-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.

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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 polyangitis (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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COMPLEX REGIONAL PAIN SYNDROME

Incidence: 6–26/100,000/year	**Indication** Chronic	**Procedure** TPE	**Recommendation** Grade 2C	**Category** III
No. of reported patients: <100	**RCT** 0	**CT** 0	**CS** 2(39)	**CR** 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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As of October 27, 2015, using PubMed and the MeSH search terms Complex Regional Pain Syndrome and plasma exchange, plasmapheresis or apheresis for reports published in the English language. References of the identified articles were searched for additional cases and trials.

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