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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 Ninth Special Issue

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Abstract

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 (TA) in human disease. In the Ninth Edition, the JCA Special Issue Writing Committee has incorporated systematic review and evidence-based approaches in the grading of evidence and categorization of apheresis indications to make recommendations on the use of apheresis in a wide variety of diseases and conditions. This edition has largely maintained the general layout and concept of a fact sheet introduced in the Fourth Edition (2007). Each fact sheet succinctly summarizes the evidence for the use of TA in a specific disease or medical condition. The Ninth Edition of the JCA Special Issue comprises 91 fact sheets and

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166 graded and categorized indications. This includes seven new fact sheets, nine new indications on existing fact sheets, and eight changes in the category for existing indications. The Ninth Edition of the JCA Special Issue seeks to continue to serve as a key resource that guides the utilization of TA in the treatment of human disease.

KEYWORDS

apheresis, extracorporeal photopheresis, immunoadsorption, plasma exchange, red blood cell exchange

1 | INTRODUCTION

The *Journal of Clinical Apheresis* (JCA) Special Issue Writing Committee is pleased to present the Ninth Edition of the JCA Special Issue. This edition was delayed a year from the scheduled 2022 release due to the tremendous impact of the COVID-19 pandemic on the apheresis community, the provision of healthcare, and the population of the entire world. The current JCA Special Issue Writing Committee was formed by the co-chairs (and ratified by the ASFA board of directors) following a formal application and selection process. Eleven committee members (six returning and five new) were selected from among 42 highly qualified applicants. Members were selected to form a geographically and clinically diverse group with a mix of senior, mid-level, and early-career individuals. The committee includes representation of multiple medical subspecialties including critical care, hematology/oncology, nephrology, pediatrics, and transfusion medicine from locations across Europe and North America. After more than 2 years of engaging collaborative 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 utilize therapeutic apheresis (TA) occasionally for the care of their patients. This latest edition of evidence-based guidelines for therapeutic apheresis is based upon a stringent review of up-to-date literature, analysis of the quality of evidence, and the strength of recommendation derived from this evidence.

The Ninth Edition of the JCA Special Issue contains fact sheets for 91 diseases/conditions (Table 1). To clarify terminology used in this table and throughout this document, "Disease" refers to a specific disease (e.g., myasthenia gravis [disease]) and "Condition" to a specific medical condition (e.g., transplantation, liver [medical condition]). The disease/condition provides the title and primary topic of the fact sheet. "Indication" refers to the use of TA in specific situations encountered in the disease/condition (e.g., for myasthenia gravis [disease], acute, short-term treatment [indication]). Each disease/condition, indication, and procedure is assigned a category (Table 2) and grade (Table 3) recommendation as in previous editions. In this edition, we have continued to use the table format at the start of each fact sheet to summarize the disease/condition name, incidence/prevalence, indication(s), procedure(s), and category and grade recommendation(s). Terminology and definitions for procedures considered in this publication have been updated with this edition (Table 4). Four diseases/conditions that are category IV, which have been described in detail in previous editions and did not have significant new evidence since the last publication were retired (Table 5). These were added to the six diseases/conditions retired in previous editions. The authors encourage the reader to refer to the last published fact sheet for information about these diseases/conditions. Sixteen diseases/conditions that underwent review in consideration for the development of a new fact sheet are listed in Table 6.

2 | METHODOLOGY

2.1 | Evidence-based approach

The Fourth Edition incorporated evidence-based medicine into well-defined and widely accepted ASFA categories and quality of the evidence.[3] In the Fifth Edition, this system was modified to revise category definitions, maintain quality of the evidence, and add the strength of the recommendation.[4] In the Sixth Edition, this was further refined to provide information on categorization, and strength of recommendation based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system,[1,2] which takes methodological quality of supporting evidence into account, while eliminating the need for "level of evidence" information used in previous fact sheets.[5] The Ninth Edition of the JCA Special Issue follows the format initiated in the Sixth Edition and continued in the subsequent Seventh and Eighth Editions[5-7] and provides information on ASFA category (Table 2) and quality of supporting evidence that forms the basis of the grading recommendation (Table 3).

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TABLE 1 Category and grade recommendations for therapeutic apheresis.

Disease/condition	Indication	Procedure	Category	Grade	Page
Acute disseminated encephalomyelitis	Steroid refractory	TPE	II	2C	95
Acute inflammatory demyelinating polyradiculoneuropathy	Primary treatment	TPE	I	1A	97
		IA	I	1B	
Acute liver failure	Acute liver failure	TPE-HV	I	1A	99
		TPE	III	2B	
	Acute fatty liver of pregnancy[a]	TPE	III	2B	
Acute toxins, venoms and poisons	Mushroom poisoning	TPE	II	2C	101
	Envenomation	TPE	III	2C	
	Other[a]	TPE/RBC exchange	III	2C	
Age related macular degeneration	Dry, high risk	DFPP	III	2B	103
Alzheimer's disease[a]	Mild or moderate	TPE	III	2A	105
Amyloidosis, systemic, dialysis related		ß$_2$-microglobulin adsorption	II	2B	107
Anti-glomerular basement membrane disease	Diffuse alveolar hemorrhage	TPE	I	1C	109
	Dialysis-independence	TPE	I	1B	
	Dialysis-dependence, no diffuse alveolar hemorrhage	TPE	III	2B	
Atopic dermatitis, recalcitrant		ECP/IA/TPE/DFPP	III	2B	111
Autoimmune dysautonomia[a]		TPE	III	2C	113
Autoimmune hemolytic anemia, severe	Severe cold agglutinin disease	TPE	II	2C	115
	Severe warm autoimmune hemolytic anemia	TPE	III	2C	
Babesiosis	Severe	RBC exchange	III	2C	117
Burn shock resuscitation		TPE	III	2B	119
Cardiac neonatal lupus		TPE	III	2C	121
Catastrophic antiphospholipid syndrome		TPE	I	2C	123
Chronic acquired demyelinating polyneuropathies	IgG/IgA/IgM related	TPE	I	1B	125
	Anti-myelin-associated glycoprotein	TPE	III	1C	
	CANOMAD/CANDA[a]	TPE	III	2C	
Chronic focal encephalitis		TPE/IA	III	2C	127
Chronic inflammatory demyelinating polyradiculoneuropathy		TPE/IA	I	1B	129
Coagulation factor deficiency and inhibitors		IA	III	2B	131
		TPE	III	2C	
Complex regional pain syndrome	Chronic	TPE	III	2C	133
Cryoglobulinemia	Severe/symptomatic	TPE/DFPP	II	2A	135
		IA	II	2B	
Cutaneous T-cell lymphoma	Erythrodermic mycosis fungoides/ Sézary syndrome	ECP	I	1B	137
	Non-erythrodermic mycosis fungoides	ECP	III	2B	
Dilated cardiomyopathy, idiopathic	NYHA functional classification II-IV	IA	II	1B	139
		TPE	III	2C	
Erythrocytosis	Polycythemia vera	Erythrocytapheresis	I	1B	141

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TABLE 1 (Continued)

Disease/condition	Indication	Procedure	Category	Grade	Page
	Secondary erythrocytosis	Erythrocytapheresis	III	1C	
Erythropoietic protoporphyria, liver disease		TPE/RBC exchange	II	2C	143
Familial hypercholesterolemia	Homozygotes	LA	I	1A	145
	Heterozygotes	LA	II	1A	
	All patients	TPE	II	1B	
Focal segmental glomerulosclerosis	Recurrent in kidney transplant	TPE/IA	I	1B	147
	All types	LA	II	2C	
	Steroid resistant in native kidney	TPE	III	2C	
Graft-versus-host disease	Acute	ECP	II	1B	149
	Chronic	ECP	II	1B	
Hemophagocytic lymphohistiocytosis		TPE	III	2C	151
Heparin-induced thrombocytopenia and thrombosis	Pre-procedure	TPE/IA	III	2C	153
	Refractory or with thrombosis	TPE	III	2C	
Hereditary hemochromatosis		Erythrocytapheresis	I	1B	155
Hyperleukocytosis		Leukocytapheresis	III	2B	157
Hypertriglyceridemic pancreatitis	Severe	TPE/LA	III	1C	159
	Prevention of relapse	TPE/LA	III	2C	
Hyperviscosity in hypergammaglobulinemia	Symptomatic	TPE	I	1B	161
	Prophylaxis for rituximab	TPE	I	1C	
Idiopathic inflammatory myopathies[a]	Anti-synthetase-syndrome	TPE	III	2B	163
	Clinically amyopathic dermatomyositis	TPE	III	2B	
	Immune-mediated necrotizing myopathies	TPE	III	2B	
IgA nephropathy	Crescentic	TPE	III	2B	165
	Chronic progressive	TPE	III	2C	
Immune checkpoint inhibitors, immune-related adverse events[a]		TPE	III	2C	167
Immune thrombocytopenia	Refractory	TPE/IA	III	2C	169
Inflammatory bowel disease	Ulcerative colitis	Adsorptive cytapheresis	II	1B	171
	Crohn's disease	Adsorptive cytapheresis	III	1B	
		ECP	III	2C	
Lambert-Eaton myasthenic syndrome		TPE	II	2C	173
Lipoprotein(a) hyperlipoproteinemia	Progressive atherosclerotic cardiovascular disease	LA	II	1B	175
Malaria	Severe	RBC exchange	III	2B	177
Multiple sclerosis	Acute attack/relapse	TPE	II	1A	179
		IA	II	1B	
	Chronic primary or secondary progressive	TPE/IA	III	2B	
Myasthenia gravis	Acute, short-term treatment	TPE/DFPP/IA	I	1B	181
	Long-term treatment	TPE/DFPP/IA	II	2B	

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TABLE 1 (Continued)

Disease/condition	Indication	Procedure	Category	Grade	Page
Myeloma cast nephropathy		TPE	II	2B	183
Nephrogenic systemic fibrosis		ECP/TPE	III	2C	185
Neuromyelitis optical spectrum disorder	Acute attack/relapse	TPE	II	1B	187
		IA	II	1C	
	Maintenance	TPE	III	2C	
N-methyl-D-aspartate receptor antibody encephalitis		TPE/IA	I	1C	189
Paraneoplastic autoimmune retinopathies[a]		TPE	III	2C	191
Paraneoplastic neurological syndromes		TPE/IA	III	2C	193
Pediatric autoimmune neuropsychiatric disorders	PANDAS/PANS, exacerbation	TPE	II	1B	195
	Sydenham's chorea, severe	TPE	III	2B	
Pemphigus vulgaris	Severe	TPE	III	2B	197
		IA/ECP/DFPP	III	2C	
Peripheral vascular diseases		LA	II	1B	199
Phytanic acid storage disease		TPE/LA	II	2C	201
Post-transfusion purpura		TPE	III	2C	203
Progressive multifocal leukoencephalopathy associated with natalizumab		TPE	III	1C	205
Pruritus due to hepatobiliary diseases	Treatment resistant	TPE	III	1C	207
Psoriasis	Disseminated pustular	ECP	III	2B	209
		Adsorptive cytapheresis	III	2C	
		TPE	IV	2C	
Red blood cell alloimmunization, pregnancy complications	Hemolytic disease of the fetus and newborn	TPE	III	2C	211
	RhD alloimmunization prophylaxis after transfusion	RBC exchange	IV	2C	
Sepsis with multiorgan failure		TPE	III	2A	213
Sickle cell disease, acute	Acute stroke	RBC exchange	I	1C	215
	Acute chest syndrome, severe	RBC exchange	II	1C	
	Other complications[a]	RBC exchange/TPE	III	2C	
Sickle cell disease, non-acute	Stroke prophylaxis	RBC exchange	I	1A	217
	Pregnancy	RBC exchange	II	2B	
	Recurrent vaso-occlusive crises	RBC exchange	II	2B	
	Pre-operative management	RBC exchange	III	2A	
Steroid-responsive encephalopathy associated with autoimmune thyroiditis		TPE	II	2C	219
Stiff-person syndrome		TPE	III	2C	221
Sudden sensorineural hearing loss		LA/DFPP/TPE	III	2A	223
Systemic lupus erythematosus	Severe	TPE	II	2C	225
Systemic sclerosis		ECP	III	2A	227

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TABLE 1 (Continued)

Disease/condition	Indication	Procedure	Category	Grade	Page
		TPE	III	2C	
Thrombocytosis	Symptomatic	Thrombocytapheresis	II	2C	229
	Prophylactic or secondary	Thrombocytapheresis	III	2C	
Thrombotic microangiopathy, coagulation mediated	*THBD, DGKE*, and *PLG* mutations	TPE	III	2C	231
Thrombotic microangiopathy, complement mediated	Factor H autoantibody	TPE	I	2C	233
	Complement factor gene mutations	TPE	III	2C	
Thrombotic microangiopathy, drug induced	Ticlopidine	TPE	I	2B	235
	Clopidogrel	TPE	III	2B	
	Gemcitabine	TPE	IV	2C	
	Quinine	TPE	IV	2C	
Thrombotic microangiopathy, infection associated	STEC-HUS, severe	TPE/IA	III	2C	237
	pHUS	TPE	III	2C	
Thrombotic microangiopathy, pregnancy associated	Pregnancy associated, severe	TPE	III	2C	239
	Extremely preterm preeclampsia, severe[a]	TPE/LA	III	2C	
Thrombotic microangiopathy, thrombotic thrombocytopenic purpura		TPE	I	1A	241
Thrombotic microangiopathy, transplantation associated		TPE	III	2C	243
Thyroid storm		TPE	II	2C	245
Toxic epidermal necrolysis	Refractory	TPE	III	2B	247
Transplantation, heart	Cellular rejection	ECP	II	1B	249
	Recurrent rejection	ECP	II	1B	
	Rejection prophylaxis	ECP	II	2A	
	Desensitization	TPE	II	1C	
	Rejection prophylaxis[a]	TPE	II	1C	
	Antibody mediated rejection	TPE	III	2C	
Transplantation, hemapoietic stem cell, ABO incompatible	Major ABO incompatible, HPC(M)	TPE	II	1B	251
	Major ABO incompatible, HPC(A)	TPE	II	2B	
	Minor ABO incompatible, HPC(A)	RBC exchange	III	2C	
	Pure red cell aplasia	TPE	III	2C	
Transplantation, hematopoietic stem cell, HLA desensitization		TPE	III	2C	253
Transplantation, intestine[a]	Antibody mediated rejection	TPE	III	2C	255
	Desensitization	TPE	III	2C	
Transplantation, kidney, ABO compatible	Antibody-mediated rejection	TPE/IA	I	1B	257
	Desensitization/prophylaxis, living donor	TPE/IA	I	1B	
Transplantation, kidney, ABO incompatible	Desensitization, living donor	TPE/IA	I	1B	259
	Antibody mediated rejection	TPE/IA	II	1B	
Transplantation, liver	Desensitization, ABOi, living donor	TPE	I	1C	261
	Desensitization, ABOi, deceased donor	TPE	III	2C	

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TABLE 1 (Continued)

Disease/condition	Indication	Procedure	Category	Grade	Page
	Antibody mediated rejection	TPE	III	2C	
	Antibody mediated rejection	ECP	III	2B	
	Immune suppression withdrawal	ECP	III	2B	
	Desensitization, ABOi	ECP	III	2C	
Transplantation, lung	Chronic lung allograft dysfunction[a]	ECP	II	1C	263
	Bronchiolitis obliterans syndrome	ECP	II	1C	
	Antibody mediated rejection	TPE	III	2C	
	Desensitization	TPE	III	2C	
Vaccine-induced immune thrombotic thrombocytopenia[a]	Refractory	TPE	III	2C	265
Vasculitis, ANCA associated	Microscopic polyangiitis	TPE	III	1B	267
	Granulomatosis with polyangiitis	TPE	III	1B	
	Eosinophilic granulomatosis with polyangiitis	TPE	III	2C	
Vasculitis, IgA	Crescentic rapidly progressive glomerulonephritis	TPE	III	2C	269
	Severe extra-renal manifestations	TPE	III	2C	
Vasculitis, other	Hepatitis B polyarteritis nodosa	TPE	II	2C	271
	Kawasaki disease[a]	TPE	III	2C	
	Multisystem inflammatory syndrome in children[a]	TPE	III	2C	
Voltage-gated potassium channel antibody-related diseases		TPE/IA	II	1B	273
Wilson disease, fulminant		TPE	I	1C	275

[a]NEW fact sheet or indication.

2.2 | ASFA categories

The definition of the four ASFA categories in this edition remain unchanged from those used since the Sixth Edition (Table 2). This allowed us to maintain a consistent approach to categorize the use of TA for diseases/conditions based on the quality of published evidence in the literature.

TABLE 2 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/Ethics Committee approval is desirable if apheresis treatment is undertaken in these circumstances.

Abbreviation: IRB, Institutional Review Board.

2.3 | Grade of recommendation

The JCA Special Issue Writing Committee recognizes the challenges in assessing study quality and translating recommendations into clinical practice. Since the Fifth Edition, the GRADE system was used to assign recommendation grades to enhance the clinical value of ASFA categories.[1,2] The JCA Special Issue Writing Committee has continued this approach in this edition (Table 3). It is important to note the grade can be used in support or against the use of the therapeutic intervention. In addition, previously designated

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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). A number of factors can affect the quality of published evidence. As an example, the quality of evidence based on a randomized control trial (RCT) can be significantly diminished by poor quality of planning and implementation suggesting a high likelihood of bias, inconsistency of results, indirectness of evidence, and/or sparse outcome data. The committee carefully took these variables into consideration while categorizing and grading diseases/conditions, indications, and procedures.

2.4 | Design of the fact sheet

The 2023 JCA Special Issue Writing Committee made only minor changes in the design of the fact sheet from the Eighth Edition based on continued positive feedback regarding the fact sheet format. The information, provided in this format is comprehensive but limited in length to facilitate its use as a quick reference. The design of the fact sheet and explanation of the information contained is included in Figure 1. Most notable is the change in location of the category and grade, which have been reversed in location to match the format presented in Table 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. References are limited to 25 and are not meant to be exhaustive but rather serve as a starting point in a search for more information.

2.5 | ASFA category assignments for 2023

The process for ASFA category assignment developed for previous editions continues to be maintained and enhanced by stringent application of evidence-based criteria to ensure consistency within and across fact sheets.

TABLE 3 Grading recommendations, strength and quality of evidence

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

Abbreviation: RCT, randomized controlled trial.
Source: Adopted from References 1 and 2.

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The JCA Special Issue Writing Committee strives to be comprehensive and systematic in assembling objective evidence for disease indications, with strength of recommendation based upon the quality of the evidence. The committee reviewed, revised, and amended indications for the use of TA in a very wide range of diseases/conditions. The membership of ASFA was also queried for potential new indications for apheresis therapy that had not been categorized in previous editions.

The process of developing new and amending old fact sheets is outlined in Figure 2. Each disease/condition was assigned to one committee member as the primary author. For existing fact sheets, a primary author reviewed any new developments in the understanding, current management, and treatment of the disease/condition as well as any changes in the evidence surrounding the use of TA as a treatment modality since the last fact sheet update. For new fact sheets, the primary author reviewed at least the past ten years of available literature. Only peer-reviewed PubMed-indexed publications available in English were considered. The primary author updated each fact sheet table, description, current management, rationale for TA, technical notes (e.g., volumes treated, frequency, replacement fluid), duration and discontinuation of treatment, and provided a maximum of 25 key references highlighting important or new studies and/or reviews (Figure 1). Two other committee members provided secondary peer-review of each fact sheet. Two fact sheets were also reviewed by external experts (see Acknowledgments). Each disease/condition, indication, and procedure was assigned an ASFA category and grade of recommendation by consensus at a face-to-face meeting and/or conference calls as described in previous editions with consistent application of evaluation criteria. This evidence-based approach is designed to achieve several objectives. First, it provides uniformity to ASFA category assignment while minimizing personal bias. Second, it provides the strength of recommendation (strong [1] vs. weak [2]) using a defined grading schema. 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.

ASFA category and grade of recommendation for diseases or conditions are summarized in Table 1. Consistent with the Eighth Edition,[6] if more than one procedure was used for the same indication within the same disease/condition, and if the assigned recommendation grade and category were identical for each procedure, it was assigned as a single indication. As an example, "Nephrogenic systemic fibrosis" is category III and grade 2C for both extracorporeal photopheresis (ECP) and therapeutic plasma exchange (TPE) and is classified as one indication. However, in keeping with the Seventh Edition,[7] if TA was used in more than one indication in the same disease/condition, each indication was assigned a recommendation grade and category. As an example, the "Transplantation, lung" fact sheet includes four indications (e.g., "chronic lung allograft dysfunction," "bronchiolitis obliterans syndrome," "antibody medicated rejection," and "desensitization"). On the fact sheet, "antibody mediated rejection" and "desensitization" are combined because they have the same procedure, category, and grade, but are counted as two unique indications for the purposes of Table 1 and Figure 3. The level of detail provided in the fact sheet is expected to give adequate clinical practice information to assist in appropriate management of patients with complex conditions.

The Ninth Edition of the JCA Special Issue introduces several naming and wording changes. For example, "Overdose, envenomation, and poisoning" was changed to "Acute toxins, venoms, and poisoning" to reflect the inclusion of mechanical hemolysis and methemoglobinemia as new indications for TA within the "other" group. Three fact sheets had name changes to reflect the current state of the role of TA in the disease/condition. This includes changes in the name of "amyloidosis, systemic" to "amyloidosis, systemic, dialysis related," "red cell alloimmunization, prevention and treatment" to "red blood cell alloimmunization, pregnancy complications," and "coagulation factor inhibitors" to "coagulation factor deficiency and inhibitors." Eponyms (such as Guillain-Barré syndrome and Refsum's Disease) were removed from the title of the fact sheets where other medical terms are preferred; however, these historical terms remain in the text of the fact sheet and are also linked to the fact sheets in the newly added index. In addition, throughout the fact sheets, language was updated to refer to heart and kidney diseases/conditions, rather than cardiac and renal respectively, to align with changing trends in nomenclature.

The total number of diseases/conditions and indications addressed in the Ninth Edition are 91 and 166, respectively. The frequency of ASFA categories and recommendation grades is illustrated in Figure 3. As with previous editions, there is a significant expansion in the number of indications (relative to the number of diseases/conditions categorized) and this is accounted for by some diseases/conditions having several categories and grade recommendations due to multiple indications within the same disease/condition, or multiple procedures used to treat the same disease/condition with different categories and grade recommendations. In a minority of diseases, there was only a single indication, for example, TPE in "thrombotic microangiopathy,

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TABLE 4 Therapeutic apheresis—terminology and methodology.

Procedure	Abbreviation	Definitions and explanations
Adsorptive cytapheresis		A therapeutic procedure in which whole blood of the patient is passed through a medical device, which contains a column or filter that shall selectively adsorb activated monocytes, granulocytes, or lymphocytes allowing the remaining leukocytes and other blood components to be returned to the patient.
$ß_2$-microglobulin adsorption		Removal of ß2-microglobulin using a whole blood adsorption column consisting of porous beads in combination with hemodialysis.
Double filtration plasmapheresis[a]	DFPP	A two-step procedure to remove pathogenic substances from plasma. Membrane plasma separation is followed by plasma filtration. Plasma filters of different mean pore sizes exist, which allow targeting preferred portions of plasma components mainly determined by molecular weight and three-dimensional structure. With this differential approach, DFPP can be used for elimination of autoantibodies, immune complexes, or lipoproteins. The term rheopheresis specifies DFPP performed using a plasma filter of medium mean pore size in the treatment of microcirculatory disorders. In principal, plasma filtration can also be performed after centrifugal plasma separation.
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.
Extracorporeal liver support systems/artificial liver support systems[a]		A heterogenous group of methods for extracorporeal blood purification/therapeutic apheresis to remove toxic substances that may play a role in liver failure pathogenesis using plasma adsorption or filtration columns and/or diffusive or convective dialysis techniques alone or in combination. Combination systems include molecular adsorbent recirculating system (MARS), fractionated plasma separation and adsorption (FPSA), or double plasma molecular adsorption (DPMAS). Bio-artifical experimental systems exist using either human-derived liver cells or porcine liver cells which, besides detoxification, may have an additional benefit by supporting metabolic and synthetic liver function.
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.
Hemoperfusion[a]		Method of extracorporeal blood purification/therapeutic apheresis using adsorber columns for whole blood adsorption. Hemoperfusion is also sometimes referred to as hemoadsorption. In sepsis, a whole blood adsorber of porous polystyrene-divinylbenzene polymer-beads has been used for cytokine removal, or a polymyxin B-immobilized fiber whole blood adsorber for endotoxin removal. Two whole blood adsorption systems exist for lipoprotein apheresis (see below).
Immunoadsorption	IA	A selective method of therapeutic apheresis in which patient plasma, after membrane based or centrifugal separation from blood, is passed through an adsorber column which has a capacity to remove immunoglobulins and immune complexes by binding them to select ligands (e.g., staphylococcal or recombinant protein A, sheep polyclonal anti-human antibodies, tryptophan, synthetic oligopeptides, monoclonal camel antibody fragments) on the backing matrix surface of membranes or beads. IA does not require replacement of plasma products. Nonspecific fibrinogen adsorption occurs with some columns. Features of available devices include single use or multiple use, and non-regenerative or regenerative adsorption capacity, the latter being capable of treating 2 to 3 plasma volumes per session, which is favorable if antibodies must be reduced to low threshold titers. The majority of adsorber columns result in broadband adsorption of immunoglobulin classes with preference for IgG. Specific adsorber columns are available for ABO-blood group antibodies (non-regenerative) or IgE (regenerative).

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TABLE 4 (Continued)

Procedure	Abbreviation	Definitions and explanations
Leukocytapheresis		A procedure in which blood of the patient or the donor is passed typically through a medical centrifuge which separates out 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 addition of replacement fluid such as colloid and/or crystalloid solution. This procedure can be used therapeutically or in preparation of blood components.
Lipoprotein apheresis	LA	The selective removal of lipoprotein particles from the blood with the return of the remaining components and without need for replacement fluids such as plasma products, thus avoiding related adverse events. A variety of methodologies with different physicochemical principles (e.g., filtration, precipitation, or adsorption) are available and include systems treating plasma (e,g., DFPP, HELP-apheresis, polyclonal-sheep-anti-apoB-immunoadsorption, dextran-sulfate plasma adsorption) and whole blood adsorption systems (e.g., using ligands consisting of dextran-sulfate or polyacrylate).
Red blood cell exchange	RBC exchange	A therapeutic procedure in which blood of the patient is passed through a medical device which separates RBCs from other components of blood. The patient's red blood cells are removed and replaced with donor RBCs.
Therapeutic plasma exchange	TPE	Plasma of the patient is separated from other components of blood, either by membrane filtration (mTPE) or centrifugation (cTPE). The plasma is removed with subsequent substitution of a replacement solution (e.g., human albumin and/or plasma) or a combination of crystalloid/colloid solution. In the literature, plasmapheresis is often used synonymously with TPE. The term high-volume TPE (TPE-HV) is used, if >2 plasma volumes are exchanged in a single session.
Thrombocytapheresis		A therapeutic procedure in which blood of the patient is passed through a medical device which separates out and removes the platelets and returns the remainder of the patient's blood with or without addition of replacement fluid such as colloid and/or crystalloid solution.

[a]The JCA Special Issue Writing Committee did not evaluate the published literature related to HP and ELSS/ALSS for the current edition; however, these procedures are included in this table to provide a more complete picture of therapeutic apheresis as they are mentioned in some fact sheets. Similar to earlier editions of the Special Issue, while DFPP is listed as a specific therapeutic apheresis procedure for some indications; in many conditions DFPP was incorporated under the broader category TPE and is not specifically noted.

thrombotic thrombocytopenic purpura." Ten new indications were added to existing fact sheets. Three are included with other pre-existing indications (e.g., "Acute toxins, venoms, and poisonings, Other" now includes mechanical hemolysis and methemoglobinemia and "Sickle cell disease, acute, Other complications" now includes bone marrow necrosis/fat embolism syndrome). The number of category I, II, III, and IV indications are 27, 44, 91, and 4, respectively (Table 1 and Figure 3). The majority of category I indications have recommendation grades of 1A to C. Category II indications are spread through the entire spectrum of recommendation grades with nearly half with recommendation grade 1A-C, and the remainder with recommendation grade 2A-C. As in prior editions, the majority (56/91 = 62%) of category III indications have recommendation grade 2C (weak recommendation with low/very low-quality evidence). Four category IV indications are listed in full fact sheets in this edition. An additional 10 retired indications with category IV recommendations, including four indications added from the 2019 Eighth Edition, are listed in Table 5. Eight indications had a change in category. Two indications were upgraded when compared to the 2019 Eight Edition: "Erythropoietic protophyria, liver disease" (III→II) and "Inflammatory bowel disease, ulcerative colitis" (III→II). Four indications were downgraded when compared to the 2019 Eight Edition: "age related macular degeneration, dry, high risk" (II→III), "babesiosis, severe" (II→III), "hyperleukocytosis" (II→III), and "red blood cell alloimmunization, pregnancy complications, RhD alloimmunization prophylaxis after transfusion" (III→IV). The "vasculitis, ANCA associated" had an in interim update published after the 2019 Eight Edition.[8] Two indications were changed when compared with the interim fact sheet: "vasculitis, ANCA associated, microscopic polyangiitis" and "Vasculitis, ANCA associated, granulomatosis with polyangiitis" (II→III for rapidly progressive glomerulonephritis and creatinine ≥5.7

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TABLE 5 Retired category IV recommendations for therapeutic apheresis.

Disease/condition	Procedure	Full fact sheet in JCA special edition
Amyloidosis, causes other than dialysis	TPE	2019
Amyotrophic lateral sclerosis	TPE	2013
Dermatomysitis/ polymyositis	TPE, ECP	2016
HELLP syndrome, antepartum	TPE	2019
Idiopathic polyarteritis nodosa	TPE	2019
Inclusion body myositis	TPE, leukocytapheresis	2013
Multifocal motor neuropathy	TPE	2019
POEMS syndrome	TPE	2013
Rheumatoid arthritis	TPE	2010
Schizophrenia	TPE	2013

Note: This table summarizes indications with category IV recommendations that are no longer included among the fact sheets in this special issue. Please refer to previous issues as specified in the chart above for more information about these indications. 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., Thrombotic microangiopathy, drug induced: category I, Ticlopidine; category IV, Gemcitabine/Quinine) or where one type of apheresis may be ineffective, while a different apheresis procedure may potentially be useful in the same disease (e.g., Psoriasis: category IV, TPE; category III, ECP or adsorptive cytapheresis).
Abbreviations: HELLP, hemolysis, elevated liver enzymes, low platelets; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes.

mg/dL; I→III for diffuse alveolar hemorrhage). In this edition, the "Vasculitis, ANCA associated" indications are now separated by pathology (e.g., "Microscopic polyangiitis" and "Granulomatosis with polyangiitis"), and both are category III regardless of creatinine levels and the presence of diffuse alveolar hemorrhage.

Sixteen diseases/conditions were considered for the creation of new fact sheets. To meet criteria for a new fact sheet, the committee required a minimum of 10 cases published in the last decade in peer-reviewed journals, ideally by more than one group. Based on these criteria, there were seven new fact sheets added to this edition (Table 1, Table 6). Three diseases/conditions were incorporated into existing fact sheets (Table 6). Six diseases/conditions were considered for the development of a new fact sheet but did not yet have sufficient published evidence to meet the criteria at the time of review. Of note among these, "transplantation, composite tissue" had evidence suggesting the effectiveness of TA but too few cases to meet the criteria for creation of a new fact sheet. These diseases/conditions may be considered in future editions as new evidence emerges (Table 6). The authors encourage practitioners of apheresis medicine to use the three McLeod Criteria[9] to assess the indication when considering the use of TA in rare diseases/conditions, which may not be categorized by the JCA Special Issue Writing Committee. These are "Plausible Pathogenesis" which implies an understanding of the disease process suggests a clear rational for TA, "Better Blood" which indicates evidence suggesting the abnormality that makes apheresis plausible is meaningfully corrected by TA, and "Perkier Patients" which means there is evidence that TA confers benefit that is clinically worthwhile and not just statistically significant.[9]

TABLE 6 Diseases/conditions considered for new fact sheets in 2023.

Incorporated as new fact sheets
Alzheimer's disease
Autoimmune dysautonomia
Idiopathic inflammatory myopathies
Immune checkpoint inhibitors, immune-related adverse events
Paraneoplastic autoimmune retinopathies
Transplantation, intestine
Vaccine-induced immune thrombotic thrombocytopenia
Incorporated into existing fact sheets
Mechanical hemolysis incorporated into acute toxins, venoms and poisons
Methemoglobinemia incorporated into acute toxins, venoms and poisons
Bone marrow necrosis/fat embolism syndrome incorporated into sickle cell disease, acute
Insufficient evidence at time of review
Autoimmune myofasciitis
Autoimmune recurrent pregnancy failure
Hyperbilirubinemia, kidney failure/bile cast nephropathy
Pancreatic transplantation
Platelet refractoriness due to human leukocyte antigen (HLA) antibodies
Transplantation, composite tissue

2.6 | General considerations

The format of the JCA Special Issue restricts the amount of information that can be provided in each fact sheet. For additional information, one textbook in the field of

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apheresis medicine which users of the Special Issue may find useful is Apheresis: Principles and Practice, 4th edition, volume 1: Therapeutic apheresis.[10] The recommendations of the ASFA "Choosing Wisely" campaign should also be considered when planning a procedure and informative communication between apheresis providers, prescribers, and patients is encouraged.[11] In Table 7, 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. Technical and special considerations regarding specific procedures are not fully described in each of the individual fact sheets and prescribers and practitioners of apheresis should ensure familiarity with potential risks associated with the use of apheresis. The authors would like to highlight several key issues in the following paragraphs.

An area of potential concern for the apheresis practitioner is the type of replacement fluid to be used during TA, notably TPE. The reader should be cognizant of the risk of coagulation factor depletion (especially fibrinogen), particularly after daily TPE use in some clinical settings.[12] Coagulation factor replacement (e.g., plasma or cryoprecipitate supplementation) may be considered in these situations.

The considerations for ECP are not fully described in the fact sheets. Typically, mononuclear cells (MNCs) are obtained from processing 1.5 L of whole blood, but volume processed varies based on patient weight, hematocrit, and method utilized. The two-step method collects and treats MNCs obtained from processing two total blood volumes. ECP treatment is often prescribed in cycles, usually two treatments per week (one cycle). Historically ECP was prescribed on two consecutive days (back-to-back) likely because of logistical necessity. The

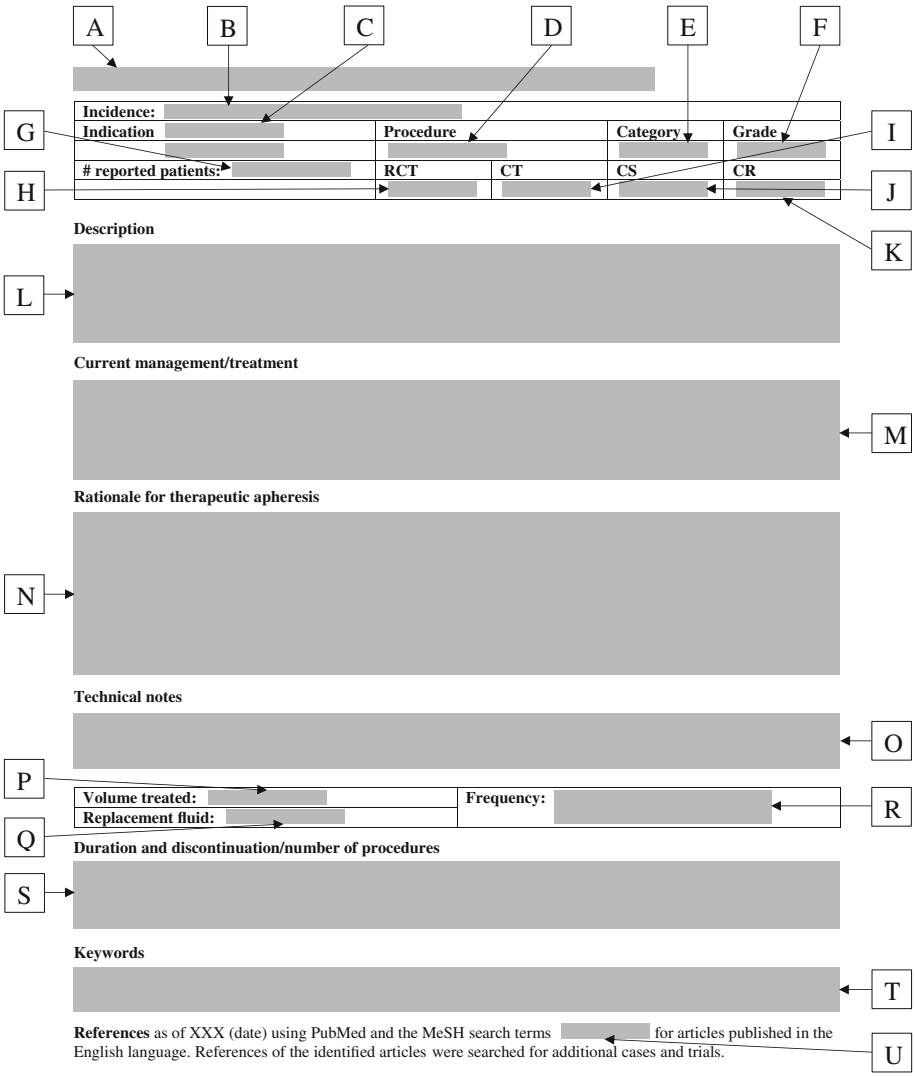


FIGURE 1 Legend on next page.

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original trials for which ECP received US Food and Drug Administration (FDA) approval, that is, treatment of cutaneous T cell lymphoma, were based on treating for two consecutive days per cycle. To date, many studies continue to treat based on this schedule; however, other studies and many in clinical practice have their cycle as two treatments per week not necessarily consecutive days. No randomized study has been published to

FIGURE 1 Fact sheet format. (A) The name of the disease/condition. (B) This section lists the incidence or prevalence of the disease. For certain diseases with insufficient data on incidence or prevalence, other terms, such as rare or unknown are used. The reader is cautioned to use this information only as a general indicator of disease incidence or prevalence. For some diseases, this may vary by geographical area. (C) The indication section refers to the use of apheresis in specific situations encountered in the disease/condition (e.g., Antibody mediated rejection [indication] in the setting of "Transplantation, heart" [disease]). (D) The type of therapeutic apheresis procedure is listed here. For certain diseases there are several apheresis based modalities available. In such instances, more than one type of procedure is listed (e.g., "Transplantation, lung" includes both TPE and ECP). (E) Category recommendation. (F) Grade recommendation is assigned to each categorized entity based on the Grading of Recommendations Assessment Development and Evaluation (GRADE) system. (G) This section lists the number of patients reported in the literature who were treated with TA. The committee used three categories: fewer than 100, between 100 and 300, and more than 300. This entry will help readers in judging how often this entity was reported to be treated with TA. However, the number of patients treated is often less important than the quality of the scientific reports. (H) Randomized controlled trials (RCT) (Patient counts should be not regarded as exact figures of all existing literature, but reflecting the magnitude of published evidence for a particular indication, and representing the major source of evidence used to assign category and grade recommendation.). 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 TA) 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). (I) Controlled trials (CT) (Patient counts should be not regarded as exact figures of all existing literature, but reflecting the magnitude of published evidence for a particular indication, and representing the major source of evidence used to assign category and grade recommendation.). The notation is similar to RCTs. Studies listed here were not randomized. The control group could be historical or concurrent to the treatment group. (J) Case series (CS) (Patient counts should be not regarded as exact figures of all existing literature, but reflecting the magnitude of published evidence for a particular indication, and representing the major source of evidence used to assign category and grade recommendation.). Number of case series (with total number of patients reported). If there were a greater than 300 patients in RCT and/or CT studies, NA (not applicable) was used. If there were more than 10 cases series with more than 200 patients >10 (>200) was used. 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. (K) Case report (CR) (Patient counts should be not regarded as exact figures of all existing literature, but reflecting the magnitude of published evidence for a particular indication, and representing the major source of evidence used to assign category and grade recommendation.). Number of case reports (with total number of patients reported). If there were greater than 100 patients in RCT, CT, and/or CS studies, NA (not applicable) was used. (L) A brief description of the disease/condition is provided here. Typically, this entry contains information on clinical signs and symptoms, pathophysiology, presentation, and the severity of the disease/condition. (M) This section provides a brief description of therapeutic modalities available to treat the disease/condition. The committee attempted to cover all reasonable modalities (e.g., medications, surgical procedures, etc.); however, this section is not intended to provide extensive discussion of any 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 TA. (N) This section discusses a rationale for TA use in the disease and summarizes the evidence in this area. (O) This section briefly describes technical details 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. (P) This section specifies commonly used volumes of plasma or blood treated. (Q) The proposed frequency of treatment is listed here. The frequency reported was typically based on data from published reports. However, in some settings, due to 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 of the treating physician. (R) The type of replacement fluid most frequently used is listed here. Terms such as plasma or albumin were used to denote the type of replacement fluid. No attempt was made to include all possible variations (e.g., 4% vs. 5% albumin; fresh frozen plasma vs. thawed plasma vs. solvent detergent plasma vs. cryoprecipitate-poor plasma). In addition, blood component modifications are listed here, if relevant (e.g., red blood cell modifications for red cell exchange). "NA" is used when there is no replacement fluid necessary (e.g., ECP). (S) This section provides basic criteria for duration and 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 employed in the particular clinical situation is suggested based upon 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. (T) Keywords are listed here. (U) The terms used to identify relevant articles are listed here.

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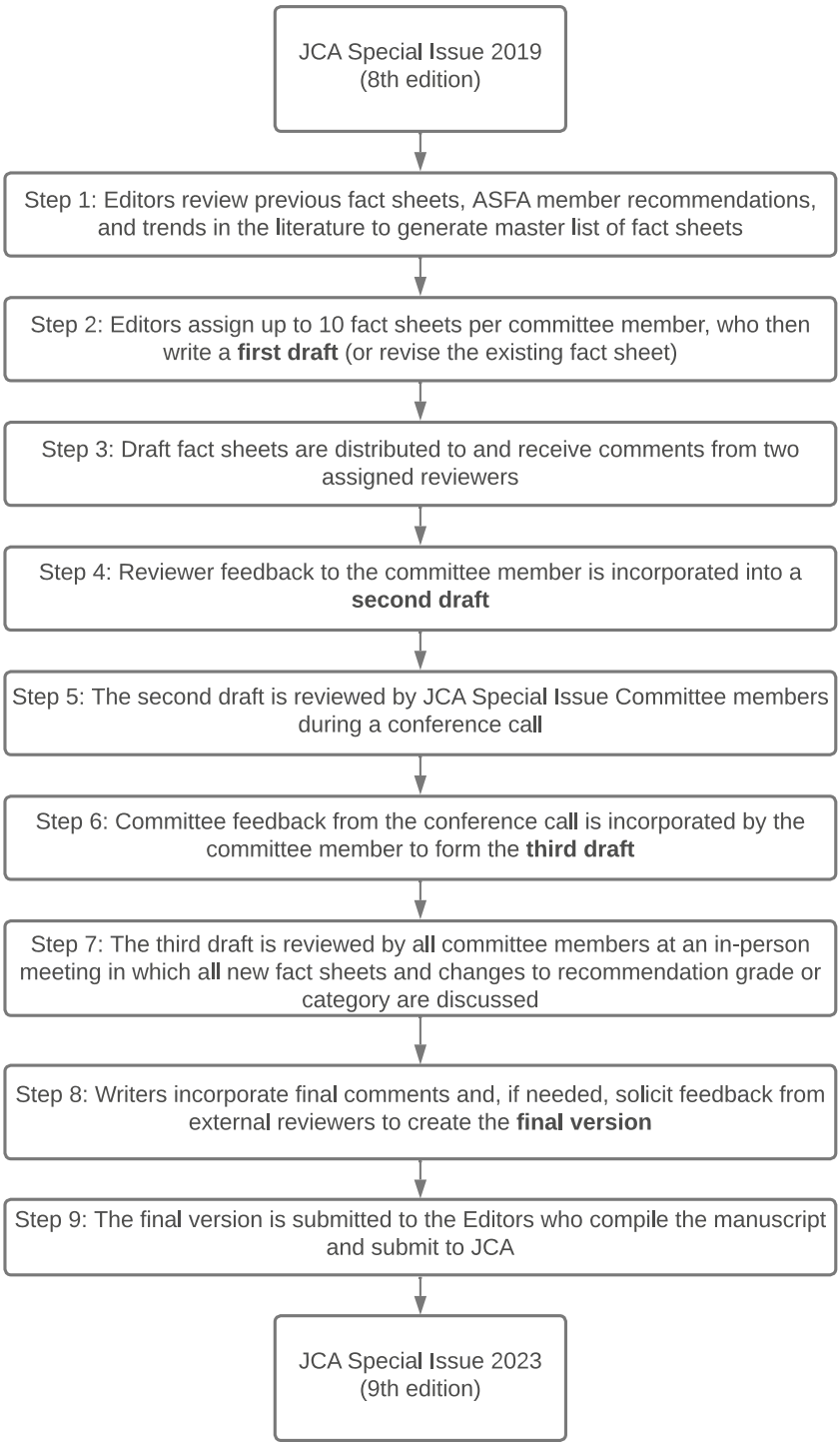


FIGURE 2 Systematic approach to fact sheet creation/revision and category/grade assignment in the 2023 Special Issue.

demonstrate lack of efficacy with treating on non-consecutive days. ECP should not be performed in patients with aphakia (absence of lens) due to increased risk for retinal damage and patients should be instructed to wear eye and skin protection for 24 h following treatment due to increased photosensitivity from the psoralen infused with the buffy coat. There may be some associated risk of venous thromboembolism in patient receiving ECP as noted in a 2018 MedWatch safety alert issued but the FDA. The reasons for these observations are not fully understood, but providers should inform their patients of the potential risk while receiving treatment with ECP.

The Ninth Edition of the JCA Special Issue provides useful information to inform practitioners about the evidence-based application of TA for a wide range of disease states. Issues related to the timing of procedures, such as emergent, urgent, and routine, are not addressed

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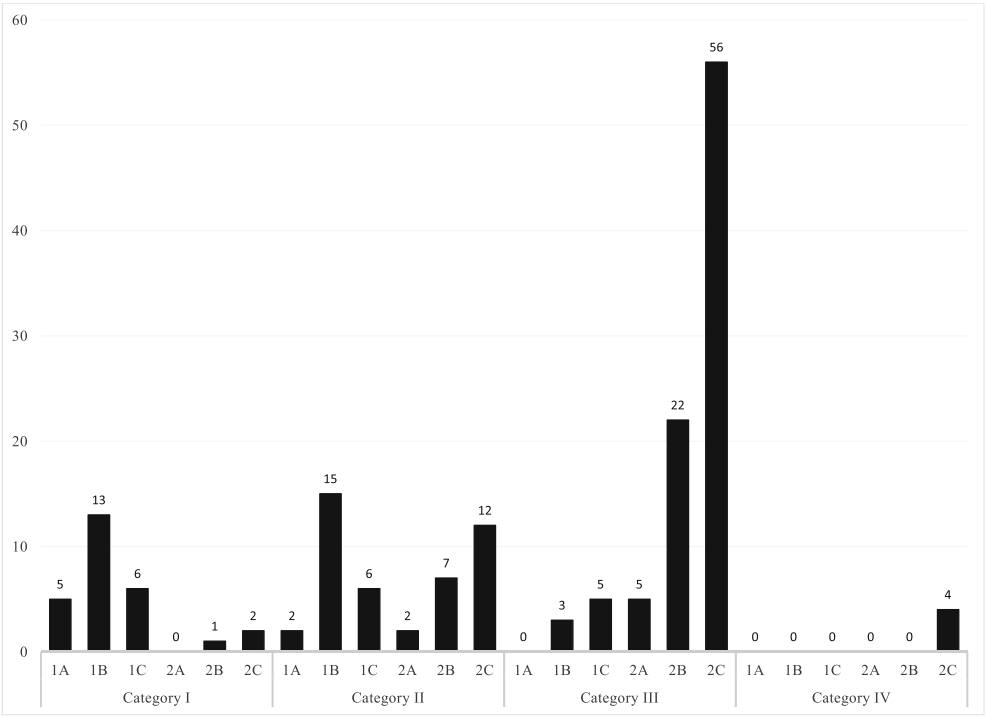


FIGURE 3 Category and grade distribution in the 2023 Special Issue.

TABLE 7 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 co-morbidities 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., emergent, urgent, routine, etc.). The location where the therapeutic apheresis will take place should be also addressed (e.g., intensive care unit, medical word, operating room, outpatient setting). If the timing appropriate to the clinical condition and urgency level cannot be met, a transfer to a different facility should be considered based on the clinical status of the patient.

Note: The above issues should be considered and explicitly discussed in a clinical note documenting the patient history, review of systems, and physical examination.

[a]The relevant ASFA fact sheet may be helpful in addressing these issues.

directly in the fact sheets given the heterogeneity of patient disease presentation and variability in the availability of apheresis. The patient's clinical condition and diagnosis, as well as availability of alternative therapies, 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.

Total blood volume and constituent volumes, such as plasma and red blood cell volumes, are used to estimate the size of an apheresis procedure. Different methods can

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be used to estimate a patient's blood volume, such as Nadler's formula, Gilcher's rule of fives, Lemmens-Bernstein-Brodsky formulas, and so forth.[13-15] These rules take into account a limited number of variables such as age, gender, height, and weight. However, additional factors influence blood volume, such as extremes of body weight or height, amputation, pregnancy, and presence of additional extracorporeal circuits. Apheresis medicine practitioners should consider the impact of such conditions when making estimates of blood volume. Furthermore, automated apheresis equipment software often requires selection of gender to calculate blood volumes, with options only limited to the binary choices of male and female. The authors encourage manufacturers to develop additional options to reflect the preferred identity of all patients undergoing apheresis procedures.

Disparities have been reported in numerous areas of health care.[16] The Center for Disease Control (CDC) defines health disparities as "preventable differences in the burden of disease, injury, violence, or opportunities to achieve optimal health that are experienced by socially disadvantaged populations."[17] Research has documented inequality across many complex dimensions including race, ethnicity, gender, sexual orientation, religion, socioeconomic status, mental health, geographic location, language, disability status, weight, and so forth.[18] Race and ethnicity are social constructs and often intertwined with other determinants of health. Furthermore, implicit and explicit bias by health care providers and health systems, including health education, contributes to health care disparities.[19,20] The authors acknowledge that inclusion of information described by determinants such as race, ethnicity, gender, and so forth in the fact sheets may contribute to health care disparities in apheresis medicine and that these determinants are unlikely to directly contribute to the therapeutic effect of apheresis (e.g., removing antibodies, sickled red blood cells, or lipids). To address these issues, language regarding determinants of health has been removed or modified to be inclusive in the fact sheets.

The COVID-19 pandemic due to the SARS-CoV-2 virus greatly influenced the practice of apheresis medicine. Many centers were impacted by supply chain and staffing challenges. Centers rapidly shifted to collect convalescent plasma from patients recovered from the virus. Based on prior experiences in infection and immune related disorders, TA procedures were used in the management of patients with COVID-19 leading to an explosion of literature on apheresis and COVID-19. This resulted in a new fact sheet for "vaccine-induced immune thrombotic thrombocytopenia (VITT)"; new indications on the "multiorgan failure, infection related" and "vasculitis, other" fact sheets; and comments on several fact sheets concerning associations with COVID-19. The index includes the terms COVID-19 and SARS-CoV-2 to identify these fact sheets.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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ACUTE DISSEMINATED ENCEPHALOMYELITIS

Incidence: <1/100,000/years (age <20 years), adult estimates not available

Indication	Procedure		Category	Grade
Steroid refractory	TPE		II	2C
# reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
	0	0	20 (154)	NA

Description

Acute disseminated encephalomyelitis (ADEM) is an acute inflammatory monophasic demyelinating disease that predominantly affects the white matter of the brain and spinal cord. It typically occurs after a fever or a viral/bacterial infection, and numerous pathogens, including SARS-CoV-2, have been implicated. Of note, compared to classical ADEM, ADEM associated with COVID-19 infection tends to have older age distribution, longer intervals between infection and ADEM symptoms, relatively poorer outcomes, and lower full recovery rate (Wang, 2022). Association between ADEM and vaccination has also been reported; however, a large case-control study did not find any increased risk of ADEM with any vaccine (Baxter, 2016). ADEM also has been reported to potentially be associated with different types of COVID-19 vaccines in a few CRs.

ADEM may occur at any age, but is most common during childhood (average age of onset 3-7 years). The pathogenesis is hypothesized to be disseminated multifocal inflammation and patchy demyelination associated with transient aberrant autoimmune response against myelin oligodendrocyte glycoprotein (MOG), myelin basic protein, or proteolipid protein. It is suggested 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 (average 12 days after the inciting event) presenting with an acute encephalopathy accompanied by multifocal neurological deficits (ataxia, weakness, dysarthria, dysphagia, cranial nerve palsies, seizures, or fever). It is usually a monophasic illness; however, recurrent or multiphasic forms have been reported, particularly in children. The prognosis is favorable, with complete recovery within weeks or months in ~60% to 90% of cases while mortality is rare (~3%). A rare hyperacute variant of ADEM, acute hemorrhagic leukoencephalitis (AHLE), is characterized by a rapidly progressive, and fulminant hemorrhagic demyelination of white matter, usually associated with severe morbidity or death. The prognosis in adults with ADEM is worse compared to children; only 10% to 46% had complete recovery and up to 25% of patients experienced at least one relapse.

The International Pediatric Multiple Sclerosis Study Group (IPMSSG) criteria for ADEM can be used to assist in making the diagnosis in pediatric patients (Krupp, 2013); however, consensus set of diagnostic criteria is not currently available for adults. Magnetic resonance imaging (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. Hemorrhagic demyelinating lesions can be seen in patients with AHLE. Electroencephalogram (EEG) may show non-specific abnormalities. Cerebrospinal fluid (CSF) analysis should be done to rule out infections. Seropositivity for anti-MOG antibody is found in 33% to 66% of pediatric cases. In patients with transverse myelitis or optic neuritis, anti-aquaporin 4 antibody should be screened for in case the patients meet the criteria for neuromyelitis optica spectrum disorder. The differentiation of ADEM from a first attack of multiple sclerosis (MS) has prognostic and therapeutic implications. Several clinical features can help distinguish ADEM from MS; these include a florid polysymptomatic presentation (typically follows a prodromal illness), lack of oligoclonal bands in the CSF, predominance of MRI lesions in the subcortical region with relative sparing of the periventricular area, and complete or partial resolution of MRI lesions during convalescence. New lesions should not appear unless a clinical relapse has occurred.

Current management/treatment

Once ADEM is diagnosed, the therapeutic aim is to stop 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 CS and CRs. There is variation in practice across centers; however, due to the postulated immune-mediated pathogenesis, treatment is based on immunomodulatory agents (Press, 2020). The widely accepted first-line therapy is the use of high-dose intravenous corticosteroids, such as methylprednisolone 10-30 mg/kg/day (maximum 1000 mg/day) for 3-5 days followed by oral prednisolone tapering over 4-6 weeks. Corticosteroids are considered effective because of their anti-inflammatory and immunomodulatory effects with additional beneficial effect on cerebral edema. IVIG, 2 g/kg total dose, given over 3-5 days, is typically reserved for patients who are steroid unresponsive, but has also been rarely used as initial or concomitant therapy. TPE can also be used as second line therapy. ADEM associated with COVID-19 infection can be managed similarly to classical ADEM; however, these patients tend to have poorer outcomes.

Rationale for therapeutic apheresis

TPE can quickly remove the presumed pathogenic autoantibodies in ADEM, such as anti-MOG antibodies. In one study, early initiation of TPE (within 15 days of disease onset) in acute attacks of CNS demyelination (including 7 cases of ADEM) was identified as a predictor of clinical improvement at 6 months (Llufriu, 2009). In patients with fulminant ADEM who respond poorly to steroid treatment and/or IVIG, TPE can be considered as second-line therapy, when used alone or in conjunction with other therapeutic modalities (Borras-Novell, 2015). In a large retrospective multicenter analysis of 228 ADEM patients, 17 patients (7%) required treatment escalation with TPE (Koelman, 2016). In this CS, either steroids, IVIG, or both preceded TPE in all patients in whom it was used.

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Technical notes

Volume treated: 1 to 1.5 TPV

Frequency: Every other day

Replacement fluid: Albumin

Duration and discontinuation/number of procedures

There is no clear recommendation on the optimal regimen of TPE in ADEM. The principal outcome of interest for TPE is acute response to treatment, rather than long-term effects on attack frequency. In one of the largest ADEM CS, TPE achieved moderate and marked sustained improvement in 40% of the patients (Keegan, 2002). Factors associated with improvement were preserved reflexes and early initiation of treatment. In most studies, clinical response was noticeable within days, usually after 2 to 3 TPEs. Treatment schedule varies between centers; most centers start with 5 to 7 procedures initially.

Keywords: acute disseminated encephalomyelitis, inflammatory demyelinating disease, acute hemorrhagic leukoencephalitis

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ACUTE INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

Incidence: 1 to 2/100,000/year

Indication	Procedure	Category		Grade	
Primary treatment	TPE	I		1A	
	IA	I		1B	
# reported patients: >300	**Procedure**	**RCT**	**CT**	**CS**	**CR**
	TPE	21 (1874)	0	NA	NA
	IA	0	1 (39)	6 (105)	NA

Description

Guillain-Barré syndrome (GBS) is an acute, typically symmetrical and ascending paralyzing disorder caused by inflammation of the peripheral nerves. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP), which comprises up to 90% of GBS cases, is an acute progressive paralyzing illness affecting both motor and sensory peripheral nerves. The remainder of GBS cases are defined by presenting pathogenic and clinical features and classified as acute motor axonal neuropathy (AMAN), acute motor-sensory axonal neuropathy (AMSAN), Miller Fisher syndrome, and acute autonomic neuropathy. Weakness or sensory impairment progresses over a period of 12 hours to 28 days before nadir is reached and may involve respiratory and oropharyngeal muscles in severe cases; mechanical ventilation is required for ∼25% of patients. Autonomic dysfunction can cause variability in blood pressure and heart rate resulting in life threatening complications. Spontaneous recovery may occur; however, neurologic complications persist in up to 20% of patients, with half severely disabled at 1 year. Mortality is estimated at 3% to 5%. GBS is usually preceded by infection or other immune stimulation that induces an aberrant autoimmune response targeting peripheral nerves and their spinal roots. Molecular mimicry between microbial and nerve antigens is a major mechanism behind the development of the disorder, as suggested by the association with *Campylobacter jejuni* infection, and the increase of GBS incidence in regions with Zika virus outbreaks. GBS has also been temporally associated with both COVID-19 infection and immunization; both IVIG and TPE have been utilized to treat these patients. However, how the immune response is shifted towards unwanted autoreactivity is still not well understood. Autoantibodies against various gangliosides, notably GM1 and GD1a, play a role, particularly in AMAN and Miller Fisher syndrome subtypes.

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 are not beneficial in the disorder. In trials using TPE and/or IVIG in GBS, patients with AIDP represented the majority compared to other variants. 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 (Plasma Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group, 1997). 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). IA avoids the need of replacing human plasma products and was used in one CT and several CS with similar efficacy as TPE. Other therapeutic modalities studied include cerebrospinal fluid filtration, DFPP, and drug targeting of complement activation. Since IVIG is readily available and a more convenient form of immunomodulatory treatment, it is frequently used as initial therapy; the typical dose is 0.4 g/kg for 5 consecutive days. A novel combination of continuous alternating IVIG and TPE termed the "zipper method" has been associated with subjectively shortened ventilator times, shortened hospital stays, and improved outcomes in a few pediatric patients with severe GBS when compared to TPE, IVIG, or other TPE plus IVIG approaches (Kesici, 2019; Nikolaus, 2022). A review of 76 patients with GBS following COVID-19 infection revealed that most patients (87%) were treated with IVIG, and only 7 underwent TPE alone or in addition to IVIG (Goudarzi, 2021). A recent meta-analysis including a total of 2474 patients from 28 trials compared efficacy of different therapies using forest plots to rank the probabilities of outcomes; TPE and IVIG were found to have significant efficacy in patients with GBS (Lin, 2021).

Rationale for therapeutic apheresis

The favored pathogenesis of GBS is autoimmune antibody-mediated damage to peripheral nerve myelin. The results of several CTs comparing TPE to supportive care alone indicate that TPE can accelerate motor recovery, decrease time on the ventilator, and decrease time to attainment of other clinical milestones. While recovery with TPE is improved, the duration of disability from AIDP remains significant. The Cochrane Neuromuscular Disease Group review of TPE in AIDP performed in 2012 and updated in 2017 concluded that TPE is an effective treatment of GBS and should be initiated within 7 days of disease onset (Chevret, 2017). 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 4 weeks. Furthermore, TPE was reported to be more cost-effective in India than IVIG (Maheshwari, 2018). There are insufficient data to conclude on the efficacy of TPE after IVIG failure. Treatment decisions must be made on a case-by-case basis.

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Technical notes

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

Volume treated: TPE: 1 to 1.5 TPV; IA: up to 3 TPV

Frequency: Every other day or daily

Replacement fluid: TPE: albumin or plasma; IA: NA

Duration and discontinuation/number of procedures

The typical TPE strategy is to exchange 1 to 1.5 plasma volumes 5 to 6 times over 10 to 14 days, some patients may need additional treatments. Considerations for IA are essentially identical.

Keywords: acute inflammatory demyelinating polyradiculoneuropathy, Guillain-Barré syndrome

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ACUTE LIVER FAILURE

Incidence: <10/1,000,000/year

Indication	Procedure	Category	Grade
Acute liver failure*	TPE-HV	I	1A
	TPE	III	2B
Acute fatty liver of pregnancy	TPE	III	2B

# reported patients: >300	Procedure	RCT	CT	CS	CR
Acute liver failure*	TPE-HV	1 (183)	2 (52)	2 (71)	NA
	TPE	2 (160)	3 (212)	NA	NA
Acute fatty liver of pregnancy	TPE	0	0	11 (170)	8 (9)

TPE-HV = TPE-high volume; *in select patients bridging to liver transplantation or with expected liver regeneration, excluding acute fatty liver of pregnancy.

Description

Acute liver failure (ALF) can develop in a normal liver or in the setting of chronic liver disease (acute on chronic liver failure, ACLF). The most common causes are acetaminophen toxicity and viral hepatitis. Other known causes include ingestion of hepatotoxins/drugs/alcohol, autoimmune hepatitis, critical illness, neoplastic infiltration, acute Budd-Chiari syndrome, and heat stroke. The mortality rate in ALF is 50% to 90% due to acute metabolic disturbances, hepatic encephalopathy, and severe coagulopathy resulting in multiple organ failure. Survival rates improve following liver transplantation (LT). ALF in children is extremely rare and can develop from metabolic disorders like Wilson's disease, intoxications like mushroom poisoning, and following viral infections (HSV, Parvo B19, SARS-CoV-2, adenovirus, etc.; Jørgensen, 2021).

The pathologic mechanism of acute fatty liver of pregnancy (AFLP) is not well established. The fetal-placental unit metabolizes free fatty acids for growth and development during pregnancy, and the placenta contains enzymes involved in the fatty acid metabolism pathway, such as long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD). The placenta breaks down triglycerides into free fatty acids which flow to the fetal compartment. Because the products of this metabolism are transferred to the fetus, defects in the fatty acid oxidation pathway of the fetal-placental unit result in accumulation of intermediate products of fatty acids and their metabolites in the maternal circulation. These are taken up by the maternal liver along with reactive oxygen species that activate inflammatory processes and cellular hepatic necrosis (Nelson, 2021). AFLP is a rare (1 out of 1000 pregnancies with abnormal liver tests) but very urgent obstetric disease and an important differential diagnosis to HELLP Syndrome (see Thrombotic microangiopathy, pregnancy associated). When combined with kidney failure, AFLP has a high mortality rate (26%; Gao, 2022).

Current management/treatment

For ALF, the standard treatment is supportive care as a bridge to recovery or LT. If LT is not available, other liver support systems have been used but none have been shown conclusively to increase survival in this cohort of patients. Liver support systems include cell-based (bioartificial) and non-cell-based therapies. Many of the cell-based liver support systems have been investigated in clinical trials (e.g., bioartificial liver, extracorporeal whole liver perfusion, extracorporeal liver assist device, and modular extracorporeal liver support). Non-cell-based therapies include TPE, albumin dialysis, liver support systems (such as molecular adsorbents recirculation system (MARS)), fractionated plasma separation and adsorption, single pass albumin dialysis, and selective plasma-exchange therapy. In the United States, the MARS system is FDA approved for use in the treatment of drug overdose and poisonings only. Other experimental approaches include hepatocyte transplantation and tissue engineering. In AFLP, delivery should be performed as soon as possible.

Rationale for therapeutic apheresis

In ALF, TPE can remove albumin bound toxins as well as unbound toxins, including aromatic amino acids, ammonia, endotoxin, indols, mercaptans, phenols, and other factors called damage-associated molecular patterns (DAMPs) responsible for organ failure, hepatic encephalopathy, and decreased systemic vascular resistance and cerebral blood flow. Studies indicate that the removal of inflammatory mediators appears to play a role in the treatment of ALF and 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. TPE has been used as adjunct or standalone therapy for bridging patients to recovery or LT. One RCT in 183 patients demonstrated higher liver transplantation-free survival to hospital discharge: 59% TPE-HV + standard care versus 48% standard care ($P<.001$) when 3 daily procedures were added to standard medical therapy in patients awaiting LT (Larsen, 2016). However, TPE-HV prior to LT did not improve overall survival compared with patients who received standard medical therapy alone. Another RCT showed reduction in the levels of pro-inflammatory cytokines and DAMPs along with amelioration of systemic inflammatory response syndrome with TPE as compared with standard medical treatment (Maiwall, 2022). TPE improved tissue microcirculation and systemic hemodynamics in patients with ALF by clearing arterial lactate and restoring the balance between plasma ADAMTS13 and von Willebrand factor. TPE has been associated with a higher 21-day transplant free-survival (75% vs. 45%; $P = .04$; Maiwall, 2022). Many centers are using combined blood purification treatments [TPE + continuous renal replacement therapy (CRRT), TPE + hemofiltration, MARS + CRRT]. This seems to have the rational that not only the liver is involved, but also the kidney and other organ systems. A retrospective analysis from 110 patients showed the use of TPE has decreased over time and the use of hemofiltration and CRRT methods has increased (Fujiwara, 2019).

For AFLP, no prospective randomized studies are available; however, the use of TPE and CRRT is described in several CS. One retrospective study in 17 patients showed that TPE plus CRRT can be used in the patient who is pregnant with excellent outcomes (5.9% mortality; Tang, 2012).

Technical notes

Since plasma has citrate as an anticoagulant and there is hepatic dysfunction, the 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. Patients should also

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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: 1 to 1.5 TPV; TPE-HV: target 8 to 12L exchange **Frequency:** Daily

Replacement fluid: Plasma or plasma/albumin

Duration and discontinuation/number of procedures

In ALF, daily TPE is typically performed for a defined period as a bridge to LT or liver self-regeneration. The biochemical response to TPE should be evaluated in laboratory values drawn the following day (≥12 hours or more after TPE) to address recirculation from the interstitium. Samples drawn immediately after completion of TPE would be expected to appear better compared to pre-TPE levels. In studies, TPE-HV was performed on 3 consecutive days. In AFLP, TPE is used until amelioration and/or delivery.

Keywords: acute liver failure, fulminant liver, hepatic failure, high volume plasma exchange

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ACUTE TOXINS, VENOMS AND POISONS

Incidence: rare				
Indication	**Procedure**		**Category**	**Grade**
Mushroom poisoning	TPE		II	2C
Envenomation	TPE		III	2C
Other*	TPE/RBC exchange		III	2C
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Mushroom poisoning	0	1 (23)	>10 (>200)	NA
Envenomation	1 (29)	1 (45)	>10 (>200)	NA
Other*	0	0	>10 (>200)	NA

*Includes drug overdose, poisoning, mechanical hemolysis and methemoglobinemia.

Description

Toxicity results from exposure to agents or toxins capable of producing tissue injury and/or organ dysfunction and includes drug overdose (accidental, intentional, or iatrogenic), envenomation, poisoning, hemolysis, and methemoglobinemia. 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. Most poisoning incidents are accidental and occur at home, most often involving children <6 years. Fortunately, serious injury is the exception, not the rule. Many of the cases in the literature are associated with suicide attempts. 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. Extracorporeal treatments may be useful for some drug poisonings. The EXtracorporeal TReatments In Poisoning (EXTRIP) workgroup provides guidance on some specific agents (https://www.extrip-workgroup.org). 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 (HP), also referred to as hemoadsorption (HA), 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

Numerous CS and CRs describe the use of apheresis (e.g., TPE, RBC exchange, combination TPE and RBC exchange) and manual blood exchange procedures in treatment of various drug overdoses, poisonings, and toxin removals, based on the knowledge of the agent. When considering the use of extracorporeal treatment, multiple factors need to be considered including the toxicokinetics of the agent, alternative treatments, patient status, and intricacies of available treatments (Ghannoum, 2018). In some cases, apheresis has been used as a supportive measure late in patient management rather than specifically for agent removal. Most reports lack adequate details to estimate the removal of the agent and patients may receive multiple treatments that contribute to the reported outcome. In some reports, the patient(s) have not survived despite apheresis treatments.

Amanita mushroom poisoning has been treated with TPE, in addition to other therapies to remove toxin including activated charcoal and forced diuresis. Large CS showed decreased mortality among patients, mostly children, treated with TPE when compared with historical controls (Jander, 2000). Very early initiation of the treatment (within the first 24-48 hours of exposure) is recommended. TPE has also been used later after ingestion in patients who develop acute liver failure as bridge to recovery or transplantation (see Acute liver disease).

TPE has also been used for toxin removal following envenomation from snakes, spiders, scorpions, and bees/wasps. A pilot RCT in patients with scorpion sting randomized 14 patients to TPE plus standard of care versus 15 patients to standard of care only and found a significantly higher number of patients in the TPE groups recovered with or without complication (p=0.045; Mostafazadeh, 2017). In regards to wasp stings, a report comparing HP + continuous venovenous hemodiafiltration (CVVHDF) versus TPE + CVVHDF, found no difference in survival (Yuan, 2016). However, a retrospective study of patients with at least 30 wasp stings observed TPE reduced mortality compared to continuous venovenous hemofiltration or HP (Liu, 2022). Patients with snakebites may develop a thrombotic microangiopathy (TMA). A systematic review of patients with snakebite associated TMA, did not find improved outcomes in patients who received TPE (Noutsos, 2020); however, TPE was initiated late in the course of treatment in some patients and studies on the use of TPE in other envenomations have shown improvement when TPE was initiated early.

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 (Mahmoud, 2021; Ibrahim, 2013). Some medications have affinity to RBCs (e.g., tacrolimus) and RBC exchange has been successfully tried under those circumstances for severe tacrolimus toxicity. Apheresis has been used when other recommended therapies have not been successful, such as methylene blue for the treatment of methemoglobinemia. The use of TPE for the treatment of mechanical hemolysis has been described in a small CS (Hei, 2009) and scattered CRs.

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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 TMA with low levels of ADAMTS13, in which case the use of plasma should be strongly considered.

Volume treated: 1 to 2 TPV **Frequency:** Daily

Replacement fluid: Albumin, plasma

Duration and discontinuation/number of procedures

TPE is usually performed daily until the clinical symptoms have abated and delayed release of toxin from tissues is no longer problematic.

Keywords: Amanita mushroom, venom, envenomation, poisoning, toxins, overdose, mechanical hemolysis, methemoglobinemia, plasma exchange, red blood cell exchange

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AGE RELATED MACULAR DEGENERATION

Prevalence: 30% of individuals over age 85

Indication	Procedure		Category	Grade
Dry, high risk	DFPP		III	2B
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	6 (433)	3 (396)	NA	NA

Description

Age-related macular degeneration (AMD) is the leading cause of severe, irreversible vision impairment in adults older than 60 years of age. Risk for the development of AMD increases with aging. It is characterized by progressive central vision loss. "Dry" (i.e., non-neovascular or atrophic) AMD is the most common form and results from the accumulation of debris (drusen) which disrupt the functional complex of the retina (i.e., photoreceptors, retinal pigment epithelium [RPE], Bruch's membrane, and choriocapillaris) and may progress to geographic atrophy, or "wet" AMD, the most severe form of the disease, characterized by abnormal choroidal neovascularization. Although an estimated 80% of patients with AMD have dry AMD, wet AMD is responsible for nearly 90% of severe vision loss. Treatment recommendations are based on a clinical classification to define early, intermediate, and late stages. Geographic atrophy of the fovea and neovascular maculopathy are always late stages. Cigarette smoking is the main modifiable risk factor. The pathogenesis of AMD has not been completely elucidated but senescence, characterized by lipofuscin accumulation in RPE cells, choroidal ischemia and oxidative damage may play a role. Mutations in the *CFH*, *C3*, *ARMS2* and *HRTA1* genes are associated with increased risk for development and progression of AMD but routine genetic testing in patients with AMD is not recommended, as gene therapy is not currently available (Apte, 2021).

Current management/treatment

Medical management of dry AMD is limited to oral supplements containing high doses of antioxidant vitamins and minerals (Evans, 2017). A variety of clinical trials for dry AMD are in process investigating anti-oxidative and anti-inflammatory drug therapies, complement inhibition, neuroprotective and cell based therapies, visual cycle modulation, mitochondrial enhancement and gene therapy (Cabral de Guimaraes, 2022). For wet AMD, intravitreous anti-vascular endothelial growth factor (VEGF) injection is first-line therapy (Veritti, 2022).

Rationale for therapeutic apheresis

Rheopheresis, a form of double filtration plasmapheresis (DFPP), removes high-molecular weight molecules (e.g., fibrinogen, LDL, α2-macroglobulin, LDL cholesterol, IgM, fibronectin, von Willebrand factor) which may impair the retinal microcirculation or contribute to a chronic inflammatory state (Kosmadakis, 2022). Rheopheresis reduces blood viscosity and erythrocyte aggregation, which may also improve RPE perfusion and function.

Early studies showed conflicting results for rheopheresis in the treatment of dry AMD. One small CT showed improvement in visual acuity in treated patients compared to untreated controls (Brunner, 2000). In contrast, an RCT published only in abstract form included patients randomized to sham-rheopheresis and showed no improvement in visual acuity in treated patients when compared to those undergoing sham procedures, suggesting the potential for a placebo effect (Swartz, 1999).

The MIRA-1 trial, the largest RCT to date, enrolled 216 patients yet failed to demonstrate a significant difference between controls and treatment groups (Pulido, 2006). Analysis revealed that 37% of treated patients and 29% of control patients were protocol violators. Excluding those subjects in a per protocol analysis, this trial demonstrated statistically significant improvement in LogMAR visual assessment with treatment, but the trial was under-powered for FDA licensure.

The largest data set is from the RheoNet registry (Klingel, 2010). Four hundred twenty-eight eyes of 279 patients with dry AMD were treated and compared to 85 eyes of 55 untreated controls. In the treated group, visual acuity gain of ≥ 1 line on Early Treatment Diabetic Retinopathy Study (ETDRS) charts was seen in 42% compared to such improvement in 26% of controls after a mean observation period of 6.75 months. Vision loss ≥ 1 ETDRS line was seen in 17% of the treated patients versus 40% of controls. These were statistically significant differences.

A subsequent RCT studied 38 patients randomized to receive 8 procedures over 10 weeks and compared them to 34 untreated controls. Best-corrected visual acuity increased from 0.61 (0.06-1.00) to 0.68 (0.35-1.00) in the treatment group ($P = .035$) (Blaha, 2013). The same group also noted reduction in the drusenoid RPE detachment area in a CT of 25 patients (Rencová, 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 morphological progression of dry AMD.

Criticism of current evidence supporting the use of rheopheresis for treatment of dry AMD include the hypothetical mechanism of action by which the apheresis procedure improves RPE function, 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 (Finger, 2010). Drusen may spontaneously regress and disappear without treatment.

In conclusion, the data is mixed and insufficient to suggest or to recommend the use of this treatment for AMD as a standard of care. Current American Academy of Ophthalmology guidelines do not include this treatment for AMD. A well-designed study that confirms the results of earlier studies is required to determine if there is robust and sustained clinical benefit of rheopheresis in the treatment of AMD.

Technical notes

The majority of CS and trials used DFPP where plasma is first separated by membrane plasma separation and then passed through a plasma filter of appropriate pore size (rheofilter) where high-molecular weight substances are removed. Centrifugal plasma separation followed by plasma filtration has been alternatively used. Currently, the filtration devices necessary for this treatment are not licensed in the United States but are available in Europe, Canada, and Asia.

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Volume treated: 0.8 to 1.5 TPV **Frequency:** 8-10 treatments (2/week) over 8-21 weeks

Replacement fluid: NA

Duration and discontinuation/number of procedures

Clinical benefit of a single course of treatment has been reported to last for up to 4 years. Repeated treatment over several years has not been systematically investigated.

Keywords: age related macular degeneration, macular degeneration, rheopheresis, plasmapheresis, double filtration plasmapheresis

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ALZHEIMER'S DISEASE

Prevalence: ~10% age 60 or older (United States)

Indication	Procedure		Category	Grade
Mild or moderate	TPE		III	2A
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	2 (389)	0 (0)	1 (7)	0

Description

Alzheimer's disease (AD) is the most common cause of dementia, accounting for 60% to 75% of all cases. Increasing age is the biggest risk factor for developing AD and other dementias. AD is characterized by progressive cognitive impairment, as well as psychiatric manifestations such as depression, delusions, and agitation. Autosomal dominant AD occurs with mutations in amyloid ß (Aß) precursor protein/*APP*, presenilin 1/*PSEN1*, and *PSEN2* genes, but is rare and mostly early-onset. The apolipoprotein E gene e4 polymorphism is a risk factor for late-onset AD, and smaller degrees of risk arise from other polygenic variants. Histopathologic characteristics of AD include the accumulation of Aß, leading to the formation of senile plaques, and by the intracellular presence of neurofibrillary tangles of tau protein. Increased cerebral production, and/or decreased clearance of Aß are thought to play a key role in AD. Although it is possible that Aß plaques and neurofibrillary tau deposits are not causal in AD pathogenesis, it is these abnormal protein deposits that define AD as a unique neurodegenerative disease.

Current management/treatment

There is still no effective treatment to reverse or slow the progression of AD. Aducanumab was controversially granted FDA approval despite early termination of clinical trials. The true impact of this drug is as yet unknown. Aducanumab enhances clearance of Aβ plaques by binding to soluble amyloid protein fibrils and oligomers. Donepezil, galantamine, rivastigmine, and memantine are focused on symptomatic treatment acting at two levels: through agonism of the cholinergic system or as antagonists of the *N*-methyl-D-aspartate receptor (NMDA-receptor). Ongoing research has focused on Aß and tau pathology aiming at decreasing Aß production, reduction of Aß load in senile plaques, enhancing Aß clearance and inhibition of tau protein hyperphosphorylation and aggregation, or potentiation of tau protein clearance.

Rationale for therapeutic apheresis

The hypothesis to use TPE with albumin replacement has several aspects. Most of Aß in the circulation is bound to albumin. Aß in the cerebrospinal fluid (CSF) is in dynamic equilibrium with plasma Aß through the blood-brain barrier and sequestration of Aß in the peripheral blood could alter such balance to induce CSF Aß to pass to plasma. Removal of plasma from a patient with AD would favor elimination of albumin-bound Aß, and possibly, other pathogenic elements (Karczewski, 2018). In addition, replacement with fresh albumin might restore the antioxidant capacity, as albumin is highly oxidized and glycated. Furthermore, a hemorheological effect on the vascular level could have a positive impact on dementia. In a RCT comparing albumin infusion with saline in patients with severe AD, Mini Mental State Examination (MMSE) improvement was seen in both groups (Hannestad, 2021).

The use of TPE was investigated in 3 clinical trials. In a pilot open-label study, 7 patients with mild to moderate AD received 3 to 5 TPE treatments over 3 weeks with a 6 months follow-up and a 1 year extension (Boada, 2009). Transient declines were seen in plasma and CSF levels of Aβ forms. Post-TPE Aß increase seen in CSF was hypothesized to be related to Aβ mobilized from brain tissue. Cognition, as determined by standard tests such as MMSE and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) did not show significant changes.

In a randomized sham-apheresis controlled study, 42 patients with mild to moderate AD were assigned (1:1) to TPE treatment or control groups (Boada, 2017). TPE (2500 to 3000 mL; ~35-45 mL/kg) with albumin replacement was performed twice weekly for 3 weeks, then weekly for 6 weeks followed by every 2 weeks for 12 weeks with 6 months follow-up. Mean CSF Aß concentrations did not exhibit substantial changes. MMSE and ADAS-Cog scores tended to be higher in the treatment group at the end of treatment and follow up periods but between-group differences were not significant.

A sham-apheresis controlled multicenter study (AMBAR study, conducted at 41 sites in the United States and Spain) evaluated the effects of TPE with different albumin (5% or 20%), and IVIG substitution (10g or 20g) in 347 patients with mild (MMSE 22-26) to moderate (MMSE 18-21) AD (Boada, 2019, 2020, 2021). TPE comprised a 6-week intensive treatment with 1 TPE (2500 to 3000 mL; ~35-45 mL/kg) per week, followed by a 12-month maintenance treatment with 1 low-volume TPE (650 to 880 mL, LVPE) per month. Patients were randomized 3:1 to TPE or sham-apheresis. ADAS-Cog and Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scores were measured as primary efficacy endpoints during treatments and at 14 months follow-up. TPE-treated patients performed significantly better in change from baseline of ADCS-ADL ($P = .03$) with a trend for ADAS-Cog scores ($P = .06$) at month 14. This result was completely driven by patients with moderate-AD with no changes in patients with mild AD. Patients treated with TPE also scored better on global assessment scores, that is, the Clinical Dementia Rating Sum of Boxes (CDR-sb) and Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) scales. The TPE-treated mild-AD cohort improved their language fluency and processing speed versus placebo at month 14. The moderate-AD cohort significantly improved short-term verbal memory. Progression of neuropsychiatric symptoms was not different between groups. Patients with mild AD showed improved QoL. CSF Aß biomarkers did not exhibit a clear disease-modifying pattern. Magnetic resonance imaging volumetric analyses and regional and statistical parametric mapping (SPM) analysis on ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) were performed (Cuberas-Borrós, 2022). TPE treatment was associated with fewer negative changes in selected subcortical structures and less metabolic decline in areas typically affected in AD compared to the placebo group. These effects were more marked in the group treated with high albumin plus IVIG compared to the low albumin groups (with or without IVIG) and in patients with moderate AD. Patients with mild AD seemed metabolically more stable over time, regardless of the treatment arm. Clinical significance of these findings is unclear. Regarding safety, 10.6% of patients suffered procedure-related adverse events, compared to 0.7% of sham patients. 52.6% of full TPE treatments were performed with central venous access, exhibiting 20.1% AEs, compared to 13.1% with peripheral access. The AMBAR study group concluded that further studies are warranted (Boada, 2020). Investigating longevity of treatment effects as well as comparative analysis of pure infusion protocols versus combination with TPE should be among the aims of these studies.

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Technical notes

Volume treated: 1 TPV

Replacement fluid: Albumin

Frequency: AMBAR study protocol: 6-weeks with 1 TPE (2500 to 3000 mL, ~1 PV) per week, followed by a 12-month maintenance treatment with 1 low-volume TPE (690-880 mL) per month

Duration and discontinuation/number of procedures

Robust conclusion on duration, discontinuation and number of procedures are not possible at this time due to the limited experience with TPE in AD.

Keywords: plasmapheresis, plasma exchange, apheresis, Alzheimer's disease

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AMYLOIDOSIS, SYSTEMIC, DIALYSIS RELATED

Incidence: up to 20% with long-term dialysis

Procedure	Category		Grade	
$ß_2$-microglobulin column	II		2B	
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	1 (36)	3 (276)	NA	NA

Description

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 tissues. The most common acquired disorders involve deposition of monoclonal immunoglobulin light chain (AL amyloidosis), serum amyloid A protein (AA amyloidosis) or $ß_2$-microglobulin (dialysis-related amyloidosis [DRA]), but several other types of amyloidosis have been described such as transthyretin, fibrinogen A α-chain, leucocyte cell-derived chemotaxin 2, and apolipoprotein A1. AL amyloidosis is associated with multiple myeloma, Waldenström's macroglobulinemia, non-Hodgkin lymphoma, and primary plasma cell dyscrasia. Acquired factor X deficiency, acquired von Willebrand syndrome, coagulopathy due to liver failure and/or vascular fragility may contribute to a bleeding diathesis in approximately one quarter of patients with AL amyloidosis. AA amyloidosis is associated with chronic infection, malignancies or inflammation (e.g., rheumatoid arthritis and hereditary periodic fever syndromes, including familial Mediterranean fever [FMF]) and predominantly affects the kidneys, leading to nephrotic syndrome and kidney failure. DRA primarily affects bones, joints and soft tissues. Little epidemiologic data have been collected on amyloidosis systematically. Amyloidosis is a relatively rare disorder with estimated incidence of 3 to 12 per million patients per year for AL amyloidosis and 2 per million per year for AA amyloidosis. DRA has become exceedingly rare with current biocompatible high-flux dialysis membranes however up to 20% of patients who require long-term dialysis (>10 years) have evidence of DRA (Portales-Castillo, 2020). Amyloidosis from causes other than dialysis is a category IV indication described in the 2019 JCA Special Issue.

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 transplant 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 the main treatment for FMF to control the periodic fevers and tissue complications, including AA amyloidosis. Immunomodulatory and anti-cytokine regimens may also be beneficial for certain inflammatory disorders that lead to AA amyloidosis. In hereditary amyloidosis, organ transplantation is performed to replace amyloidotic organs or, in the setting of liver transplantation, reduce abnormal protein production. More recently, therapeutics have been developed to decrease hepatic synthesis of transthyretin, including a *2'-O-methoxyethyl*-modified antisense oligonucleotide (inotersen) as well as an RNA interference therapeutic agent (patisiran). In AA amyloidosis, initially eprodisate had some promising findings as a targeted therapy to slow the progression of kidney disease; however, a phase III clinical trial failed to meet its primary endpoint. DRA can be managed with aggressive dialysis using membranes and treatment protocols that optimize clearance of $ß_2$-microglobulin; however, kidney transplantation is the treatment of choice. Amyloid recurs in the transplanted kidney in 15% of cases reported in the literature. Bone and joint complications of DRA are managed symptomatically.

Rationale for therapeutic apheresis

A $ß_2$-microglobulin-adsorbent column that connects to a dialyzer in tandem for direct hemoperfusion for DRA has been commercially available in Japan since 1996, in Europe since 2013, and in the United States since 2015. Its use has been primarily limited to Japan, where there is a larger population of patients receiving long-term dialysis (>10 years) due to lower rates of kidney transplantation and improved dialysis mortality rates. Criteria in Japan to qualify for the $ß_2$-microglobulin column include: (1) biopsy confirmed amyloid deposition due to $ß_2$-microglobulin, (2) dialysis vintage >10 years and a history of carpal tunnel surgery, and (3) bone cysts present on imaging. An RCT of 36 patients demonstrated a significant improvement in activities of daily living (ADL), stiffness, and pain scores in the $ß_2$-microglobulin column group ($n = 18$) after 2 years (Gejyo, 2004). In a study of 17 patients, each acting as their own control, pinch strength and ADL scores were improved after one year of treatment (Abe, 2003). A survey of 138 institutions revealed that attending physicians considered $ß_2$-microglobulin adsorption column treatment to be at least partially effective in greater than 70% of patients ($n = 345$) (Gejyo, 2013). In a large study of 1314 patients undergoing dialysis more than 10 years, quality of life surveys were lower in those with DRA than those not diagnosed with DRA. This study also found in 2 year follow up, that 75 patients with DRA who were routinely treated with a $ß_2$-microglobulin column had significantly less decline in quality of life scores than 147 patients with DRA who received conventional dialysis therapy alone (Tsuruya, 2021). CRs and small CS have described the use of TPE in patients with amyloid associated disorders. Due to concurrent immunosuppressive therapies, limited information on TPE procedures performed, and failure to establish improvement in symptoms, the relative benefit of TPE is not clearly discernible. No data exist supporting the use of TPE for neuropathy or other complications associated with AL amyloidosis, AA amyloidosis or DRA.

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Technical notes

Volume treated: 1 to 1.5 TPV **Frequency:** 3x/week with hemodialysis

Replacement fluid: NA

Duration and discontinuation/number of procedures

For DRA, clinical trials have reported outcomes after 1 or 2 years of treatment, but a survey of 345 patients reported a treatment period of 3.5±2.7 years (range 9 months-11 years) (Gejyo, 2013). Given continuous $ß_2$-microglobulin production and accumulation in patients on long-term dialysis, likely the use should be ongoing/indefinite.

Keywords: amyloid, amyloidosis, systemic amyloidosis, light chain amyloidosis, $ß_2$-microglobulin, dialysis-related amyloidosis, familial Mediterranean fever

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ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE

Prevalence: 10/1,000,000 hospitalized pts (United States)

Indication	Procedure		Category	Grade
DAH	TPE		I	1C
Dialysis-independence	TPE		I	1B
Dialysis-dependence*, no DAH	TPE		III	2B
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	1 (17)	0	>10 (>200)	NA

DAH = diffuse alveolar hemorrhage; *at presentation, Cr ≥5.7 mg/dl or need for dialysis

Description

Anti-glomerular basement membrane (anti-GBM) disease, formerly called Goodpasture's syndrome, is defined as the presence of small-vessel vasculitis which affects the glomerular capillaries, pulmonary capillaries, or both along with anti-GBM autoantibody deposition. The disease most commonly presents with rapidly progressive glomerulonephritis (RPGN). Patients may experience a non-specific prodrome of fatigue, weight loss, and low-grade fevers. Kidney biopsy shows a crescentic glomerulonephritis with the pathognomonic immunofluorescence finding of linear IgG deposition along the glomerular capillaries. Pulmonary hemorrhage occurs in 25% to 60% of patients, with presentations ranging from mild hemoptysis to life-threatening diffuse alveolar hemorrhage (DAH). Anti-GBM antibodies are directed against the non-collagenous domain of the α3 chain of type IV collagen, causing activation of the complement cascade, resulting in tissue injury. New antigens have been identified in anti-GBM disease, including peroxidasin (similar structure to myeloperoxidase) and laminin-521 (a component of the mature GBM). Anti-GBM disease was first described in 1919 during the Spanish Influenza pandemic, and clustering of cases supports environmental triggers, including drugs, environmental toxins and infections. A report from London described a fivefold increased incidence of anti-GBM disease during the COVID-19 pandemic. At disease onset, approximately half will have severe or end stage kidney failure; the proportion of crescents observed on biopsy correlates with the degree of kidney failure at presentation. Almost all patients have circulating anti-GBM antibodies in their blood at the time of diagnosis; up to 30% to 40% will also have detectable anti-neutrophil cytoplasmic antibody (ANCA). Presenting with both anti-GBM and ANCA antibodies is known as "double-positivity," and while the initial presentation is similar to classic anti-GBM disease the clinical course can be more severe and is more likely to relapse. Anti-GBM disease can also occur post-transplant in approximately 5% of patients with Alport syndrome, a hereditary nephritis due to variants in the genes encoding type IV collagen.

Current management/treatment

Prognosis of classical anti-GBM disease is strongly correlated to prompt initiation of therapy. Treatment includes the combination of TPE, cyclophosphamide, and corticosteroids for rapid clearance of antibodies and prevention of further antibody production (Rovin, 2021). While RCTs have not been conducted, there is compelling evidence that morbidity and mortality have improved since the introduction of TPE. It is critical that TPE is implemented early in the course of anti-GBM nephritis. Several CS have demonstrated that most patients with creatinine <5.7 mg/dL recover kidney function with treatment. Those with an initial creatinine ≥5.7 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. This is in accord with Kidney Disease: Improving Global Outcomes (KDIGO) conclusions on a very poor prognosis of recovery of kidney function if a patient requires dialysis at presentation and their kidney biopsy shows 100% crescents or more than 50% glomerulosclerosis. Such patients may not benefit from TPE and risk versus benefit should be carefully considered. DAH can be rapidly fatal or may have relatively mild manifestations; 90% of affected patients will respond. Therefore, a low threshold for initiating TPE is warranted in the presence of DAH. IA and DFPP with small pore plasma filters have been used in small CS with efficient removal of anti-GBM antibodies (Biesenbach, 2014). Clinical benefit appears to be comparable to TPE, though randomized comparative studies have not been performed. In a recent US analysis of 964 patients who were admitted in hospital with anti-GBM disease, the mean age of patients was 54 years, 52% required renal replacement therapy, and only 39% received TPE during hospitalization (Kaewput, 2020). The in-hospital mortality rate was 7.7 per 100 admissions. The factors associated with increased in-hospital mortality were age older than 70 years, sepsis, the development of respiratory failure, circulatory failure, kidney failure, and liver failure, whereas the factors associated with decreased in-hospital mortality were more recent year of hospitalization and the use of TPE.

CRs of using rituximab either in addition to these therapies or in place of cyclophosphamide have been reported, however, the role of rituximab needs to be established. Relapse is rare for classic anti-GBM disease, therefore chronic immunosuppression is generally not required, except in patients with ANCA and anti-GBM antibodies. If kidney recovery is not achieved within the first month of therapy, it is unlikely to occur and patients may ultimately need kidney transplant once anti-GBM antibodies are undetectable.

Rationale for therapeutic apheresis

Because of the knowledge that this disorder was associated with the presence of circulating, pathologic antibodies and the poor prognosis with treatments available at the time (90% would either die or require long-term hemodialysis), TPE was applied for treatment in the early 1970s. Early experimental studies confirmed that the anti-GBM antibodies are directly pathogenic when applied to experimental animal models. A single RCT involving a small number of patients demonstrated maintained kidney function and improved survival (Johnson, 1985). Additional benefits include a more rapid decline in anti-GBM antibody and resolution of hemoptysis. Reviews suggest that avoidance of end stage kidney disease or death will be achieved in 40% to 45% of patients.

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Technical notes

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

Volume treated: 1 to 1.5 TPV

Replacement fluid: Albumin; plasma when DAH present

Frequency: Daily at initiation with subsequent reduction of frequency according to individual clinical course, up to 10 treatments might be necessary

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 to 20 days. It is generally recommended that the treatment begin daily for 2 to 3 weeks or until the anti-GBM level is undetectable (Rovin, 2021). At the end of the 2-3 week regimen, the need for further TPE is dependent upon the patient's clinical status and antibody titer. If DAH persists, or antibody titers are rebounding, the TPE regimen should be extended, at which time a taper to every other day may be considered.

Keywords: Goodpasture's syndrome, diffuse alveolar hemorrhage, rapidly progressive glomerulonephritis, anti-GBM antibodies, ANCA, plasma exchange, immunoadsorption, double filtration plasmapheresis

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ATOPIC DERMATITIS, RECALCITRANT

Incidence: ~20% of children and ~10% of adults; recalcitrant is rare

Procedure	**Category**		**Grade**	
ECP/IA/TPE/DFPP	III		2B	
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
ECP	1 (20)	2 (45)	11 (121)	NA
IA	0	6 (100)	3 (19)	NA
TPE/DFPP	0	1 (9)	0	1 (1)

Description

Atopic dermatitis (AD), or eczema, is the most common chronic relapsing skin disease seen in infancy and childhood. It affects up to 20% of children worldwide and frequently occurs in families with other atopic diseases. Infants with AD are predisposed to development of allergic rhinitis and/or asthma later in childhood, a process called "atopic march." The pathogenesis of AD skin inflammation includes genetic and environmental factors, skin barrier dysfunction, microbial balance, and environmental triggers. AD is characterized by T cell dysfunction. Patients may have elevated immunoglobulin E (IgE) levels, though the relevance of IgE as a trigger for AD is unknown. AD may have a transient presentation early in life, but may also have a relapsing-remitting to chronic persistent course and active AD beyond childhood is common.

Current management/treatment

The treatment of AD requires a systematic, multifaceted approach that incorporates skin hydration, topical anti-inflammatory therapy (including corticosteroids and calcineurin inhibitors), identification and elimination of flare factors (especially foods), and, if necessary, systemic therapy. Several guidelines on the overall management of patients with AD have been published. A number of biologic therapies have been (or are being) evaluated in patients with AD. Dupilumab is a human monoclonal antibody that inhibits interleukin-4 (IL-4) and IL-13 signaling as an IL-4Rα antagonist and is approved for the treatment of moderate-to-severe AD. In refractory disease, phototherapy [ultraviolet A1 (UVA1), UVB, or psoralen and UVA (PUVA)] can be used. Combination therapies are used to minimize side effects, especially from immunosuppressive drugs. In AD, the SCORAD (SCORing Atopic Dermatitis) scale and EASI (Eczema Area and Severity Index) are clinical tools for assessing the extent and severity of and are used for evaluating treatment success.

Rationale for therapeutic apheresis

Given the side effects of third-line therapies including immunosuppressive agents and phototherapies, ECP is used as a non-toxic and non-immunosuppressive alternative. Since 1994, CS and controlled studies in >100 patients have been published with ~50% to 70% of patients having a favorable response to ECP, requiring at least 6 cycles for a response. In one RCT, equivalence to cyclosporine therapy was shown (Koppelhus, 2014). ECP may be considered in a patient with AD who fulfills the following criteria: (1) a diagnosis of severe AD of at least 12 months duration, (2) SCORAD > 45, (3) resistance in the last 12 months to all first-line therapies, including topical steroids and topical calcineurin inhibitors, and (4) resistance to one form of phototherapy, dupilumab, or either systemic steroids or cyclosporine as second-line therapy (Knobler, 2020).

IA decreases levels of IgE significantly. Both non-specific and IgE-specific columns have been used (Kasperkiewicz, 2018; Reich, 2019). Of note, only a short-term decrease of the serum IgE, followed by rapid 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.

TPE and DFPP are used to reduce IgE and immune complexes from patients' blood. For DFPP, there is one CT showing a significant improvement in symptoms (Kim, 2013).

Technical notes

Volume treated: ECP: varies; IA: 2 to 4 TPV; TPE and DFPP: 1 to 2 TPV

Replacement fluid: TPE/DFPP: albumin

Frequency: ECP: 1 cycle of 2 procedures every 2 weeks for 12 weeks, then tapering; IA: series of up to 3 to 5 consecutive daily IA every 4 weeks up to 10 to 12 total; TPE and DFPP: weekly

Duration and discontinuation/number of procedures

The initial ECP treatment for AD is typically one cycle (2 treatments) every 2 weeks for 12 weeks, thereafter ECP treatment regimen depends on individual response, but is typically performed every 3-4 weeks, and then tapered to every 6-12 weeks before stopping; however, protocols have varied. Several studies have performed ECP treatments on consecutive days and many centers continue to use this practice. Relapse

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could be treated by returning to the interval frequency of the previously effective treatment schedule. In IA, 10 to 12 treatments are performed over 4-6 weeks.

Keywords: recalcitrant atopic dermatitis, immunoadsorption, plasma exchange, extracorporeal photopheresis

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AUTOIMMUNE DYSAUTONOMIA

Incidence: unknown

Procedure	Category		Grade	
TPE	III		2C	
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	5 (30)	17 (18)

Description

Autoimmune dysautonomia covers heterogeneous acquired syndromes exhibiting symptoms related to the autonomous nervous system. Autoimmune autonomic ganglionopathy (AAG) is typically positive for anti-ganglionic acetylcholine receptor (gAChR) antibodies. AAG is characterized by various symptoms such as central nervous system involvement, peripheral sensory neuropathy, endocrinopathy, as well as autonomic dysfunction. Typical autonomic symptoms of AAG are severe orthostatic hypotension, constipation, and urinary disturbances. Small fiber neuropathy (SFN) is the result of damage to peripheral nerves, including those that are small and myelinated (Aδ), as well as those that are unmyelinated (unmyelinated C fibers). In SFN, small somatic and autonomic fibers can be affected which may control thermal and pain perception as well as autonomic and enteric functions. For this reason, patients with SFN can present with autonomic and/or somatic symptoms (see also Chronic regional pain syndrome). Postural orthostatic tachycardia syndrome (POTS) is the most prevalent chronic cardiovascular dysautonomia. POTS is characterized in adults by a sustained heart rate increment of ≥30 beats/min within 10 minutes of standing or head-up tilt without orthostatic hypotension. The cerebral hypoperfusion and reflex sympathetic activation of POTS manifests as fatigue, syncope, palpitations, lightheadedness, dizziness, nausea, headaches, exercise intolerance, and sleep disturbances. Comorbidities include Ehlers-Danlos syndromes, mast cell activation syndrome, sensory neuropathy, and other autoimmune disorders (e.g., systemic lupus erythematosus or Sjogren syndrome). The etiology of POTS is largely unknown but acetylcholine receptor (AchR) antibodies have been identified in more than 10% of POTS cases (Theiben, 2007). Autoantibodies against adrenergic, cholinergic, muscarinic, and *N*-methyl-D-aspartate (NMDA) receptors have also been identified in POTS patient sera. Preceding viral illness has been described in about 25% of POTS cases, but it has also been reported after HPV vaccination (Benarroch, 2012; Blitshteyn, 2017). Autoimmune dysautonomia symptoms, particularly those of SFN and POTS, have also been reported after COVID-19 vaccination and as a component of post-COVID-19 syndrome (Blitshteyn, 2021; Hoeijmakers, 2022).

Exacerbating factors of orthostatic intolerance and include heat exposure, physical exertion, prolonged recumbency, as well as diuretic and vasodilator medications. Diagnostic evaluation requires exclusion of cardiac causes of tachycardia, alternative autonomic neuropathies, endocrine causes of hyperadrenergic states, and generalized cardiovascular deconditioning.

Current management/treatment

Standard orthostatic intolerance interventions include patient education and behavioral conditioning, increased sodium and water intake, physical counter-maneuvers to increase mean arterial pressure, use of support garments, graded exercise training, and tailored pharmacotherapy with fludrocortisone, midodrine, droxidopa, beta-adrenergic blockers, and/or pyridostigmine. Trials of steroids, TPE, IVIG, and rituximab have been performed if autoimmunity was considered the main etiology. Pre- and post-intervention symptom assessments may include autonomic function tests, orthostatic hypotension questionnaires, and neuropsychologic exam and test batteries.

Rationale for therapeutic apheresis

Given the favorable outcomes of TPE in other immune-mediated conditions, the removal of autoantibodies may improve autoimmune dysautonomia symptoms. Presence of circulating agonistic autoantibodies against G-protein-coupled receptors activating adrenergic, muscarinic, and nociceptin receptors had predictive value for the severity of symptoms in patients with POTS. TPE induced decreases in NMDA and AChR antibody levels have been correlated with improvement in POTS and AAG in CRs and CS, though treatment approaches vary significantly. Subsequent use of maintenance TPE has been described and has been similarly associated with aforementioned gains. Given the transient nature of antibody depletion, TPE should be used in conjunction with medications such as steroids or rituximab to slow antibody-production.

Technical notes

Replacement volumes vary in the literature. Total fluid balance should be set ≥100%, as needed to address the patient's volume status and baseline blood pressure. TPE should not be used as a monotherapy.

Volume treated: 1 to 2 PV

Frequency: POTS: 2 to 3 times per week; AAG: 1 to 5 times per week

Replacement fluid: Albumin

Duration and discontinuation/number of procedures

For POTS, series of 4 to 6 TPE over two weeks have been reported. Symptoms are reported to reoccur 4 weeks to 6 months after cessation of TPE. Maintenance TPE (1-4 procedures performed every 2-3 weeks) has been proposed. Progressive spacing of maintenance procedure

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frequency has been suggested. For AAG, 1 to 5 TPE performed per week over the course of 1 to 6 weeks have been reported. Maintenance TPE (1-2 procedures performed every 4 weeks) has been described.

Keywords: postural orthostatic tachycardia syndrome, autoimmune autonomic ganglionopathy, small fiber neuropathy, plasma exchange, plasmapheresis, orthostatic intolerance

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AUTOIMMUNE HEMOLYTIC ANEMIA, SEVERE

Incidence: <1/100,000/year

Indication	Procedure		Category	Grade
Severe cold agglutinin disease	TPE		II	2C
Severe warm autoimmune hemolytic anemia	TPE		III	2C
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
Severe cold agglutinin disease	0	0	2 (6)	35 (38)
Severe warm autoimmune hemolytic anemia	0	0	3 (14)	37 (41)

Description

Autoimmune hemolytic anemia (AIHA) represents a group of disorders in which autoantibodies mediate either intravascular hemolysis by the terminal lytic complex (C5b-C9) or extravascular destruction of red blood cells in the spleen by the macrophage-phagocytic system. Patients present with fatigue, jaundice, and dyspnea, or may have no symptoms if well compensated. Laboratory findings include signs of immune hemolysis (anemia, hyperbilirubinemia, elevated serum lactate dehydrogenase, reduced haptoglobin, and polychromasia/anisocytosis on peripheral smears) which are often associated with a positive direct antiglobulin (Coomb's) test (DAT). Results of the DAT may be misleading as it can be positive in healthy subjects and may be negative in approximately 10% of patients with AIHA.

AIHA is classified into warm autoimmune hemolytic anemia (WAIHA) and cold agglutinin disease (CAD)/cold autoimmune hemolytic anemia (CAIHA). Warm autoantibodies include IgG or IgA hemolysins that react optimally at 37°C and may demonstrate pan-reactivity or relative specificity to RBC antigens. WAIHA may be idiopathic (30%), associated with underlying autoimmune diseases, lymphoproliferative disorders, infections, following hematopoietic stem cell/solid organ transplantation, or 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 to 5°C and may be directed against the I/i antigens. It is typically seen in the post-infectious setting (polyclonal autoantibodies) or in lymphoproliferative disorders (monoclonal autoantibodies). The cold-reactive IgM autoantibody produced after *Mycoplasma pneumoniae* infection typically has anti-I specificity, whereas the autoantibody associated with Epstein-Barr virus infection (infectious mononucleosis) demonstrates anti-i specificity. In CAD, the DAT is positive with anti-C3b only. The severity of hemolysis is influenced by the autoantibody titer, avidity to RBC antigens, ability to fix complement, and, most importantly for cold autoantibodies the thermal amplitude (highest temperature at which the antibody reacts with its cognate antigen). A cold autoantibody with high thermal amplitude can be active within the range of temperatures attainable in vivo. AIHA is considered severe when the hemoglobin falls below 8.0 g/dL and transfusion is required with an interval ≤7 days; there are severe symptoms of anemia and hemoglobin instability (Jäger, 2020).

Current management/treatment

Given its overall rarity, there are limited randomized therapeutic trials; treatment is based on expert opinion and retrospective studies. Prednisone (1 mg/kg/day) remains first-line therapy for WAIHA, with addition of rituximab considered early in severe cases lacking prompt response. Prednisone suppresses antibody production and down-regulates Fc-receptor-mediated hemolysis in the spleen. Rituximab has documented short-term efficacy but there remains limited information on long-term efficacy or ability to prevent the need for other treatment. The RAIHA RCT showed efficacy of prednisone plus rituximab as first-line therapy in WAIHA (Michel, 2016). Splenectomy, while underutilized, remains an effective therapy and may be considered if corticosteroids and rituximab fail. Other modalities used in refractory cases include IVIG, cyclophosphamide, vincristine, mycophenolate mofetil, azathioprine, sirolimus, and monoclonal antibodies. One CR showed efficacy with eculizumab (Ma, 2016).

In patients with CAD and severe hemolytic anemia, treatment primarily involves avoiding exposure to cold. Sultimlimab, a new IgG4 humanized monoclonal antibody, was approved in February 2022 by the FDA for treatment of CAD in adults. It inhibits the classical complement pathway at C1s, preventing deposition of complement opsonin on the surface of red blood cells, thereby inhibiting hemolysis (Dhillon, 2022). In patients with severe disease, the most effective and best-evaluated treatment has been rituximab, which has been recommended as first-line therapy, although complete and sustained remissions are uncommon. The Nordic prospective nonrandomized multicenter trial showed efficacy of bendamustine plus rituximab in 32 of 45 patients with CAD (Berensten, 2017). Bortezomib has also shown efficacy. In situations of life-threatening hemolysis and anemia despite first-line treatment, rescue treatments with blood transfusions via a blood warmer, eculizumab, extracorporeal column immuno-absorption apheresis, and TPE have been described. Prednisone and splenectomy are usually ineffective, because the liver is the dominant site of destruction of C3b-sensitized RBCs. Secondary CAD typically responds well to anti-lymphoma chemotherapy. Several ongoing trials of novel therapies for both warm and cold AIHA are ongoing (Xiao, 2022).

Rationale for therapeutic apheresis

TPE may remove pathogenic immune complexes, activated complement components, and circulating autoantibodies; it is typically utilized in patients with fulminant hemolysis unresponsive to RBC transfusion and/or steroid therapy. TPE may temper the disease course until more aggressive immunosuppression takes effect. In WAIHA, CRs and CSs have shown conflicting results with the use of TPE. In one CS utilizing TPE in the setting of severe WAIHA, TPE versus no TPE did not demonstrate differences in increase in hemoglobin levels post-transfusion (Ruivard, 2006). Two retrospective studies reported on the use of whole blood exchange for severe AIHA (Li, 2015; Jiang, 2022). IgM autoantibodies in CAD are primarily intravascular and thus might effectively be removed by TPE. TPE might also be beneficial in patients with CAD before surgeries requiring hypothermia (Barbara, 2013). One CR described the management of CAD in off-pump coronary artery bypass surgery with an intravascular warming catheter instead of TPE (Tholpady, 2016). Response after TPE is often temporary, depending on the characteristics and rate of autoantibody production and thus, should be combined with immunosuppression. CRs have claimed success using TPE as a "primer" for IVIG, cyclophosphamide treatment, or bortezomib (e.g., synchronization of 1 to 3 daily sessions of TPE followed by pulse treatments with immunosuppression). One meta-analysis was

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published evaluating the use of TPE in adults with AIHA; thirteen RCTs from Chinese databases including 906 patients were evaluated and demonstrated increased incidence of remission and improvement of hematologic parameters in patients treated with TPE (Deng, 2020). These studies are not available for formal review through PubMed and are therefore not included in the table. Limitations to the study include lack of distinction of warm/cold AIHA, and publication bias.

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. In CAD, use of plasma as a replacement fluid may be harmful, supplying the circulation with fresh complement source.

Volume treated: 1 to 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 immunosuppressive therapy takes effect.

Keywords: autoimmune hemolytic anemia, cold agglutinin disease, direct antiglobulin test, plasma exchange, warm autoimmune hemolytic anemia

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BABESIOSIS

Incidence: endemic in United States Northeast and upper Midwest regions

Indication	Procedure		Category	Grade
Severe	RBC exchange		III	2C
# reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
	0	1 (28)	9 (157)	NA

Description

Babesiosis is a tick-borne zoonosis caused by an intraerythrocytic protozoan. The species that most commonly infect humans are *B. microti* (the predominant US pathogen), *B. duncani*, *B. divergens, B. venatorum*, and *B. crassa-like pathogen*. Ninety-five percent of cases in the United States are in the Northeast and upper Midwest, 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 in the summer months. Babesiosis can be also transmitted by blood transfusion (typically RBCs from asymptomatic blood donors), solid organ transplant, and vertical mother-to-child infection. The incubation period is usually 1 to 4 weeks, with longer incubation periods (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, (2) mild-moderate illness, the most common presentation (characterized by malaise, fatigue, intermittent fever and chills) and (3) severe disease, which generally occurs in people with underlying immunosuppressive conditions (e.g., HIV, malignancy, immunosuppressive medication, or asplenia) or with risk factors such as age >50 and simultaneous co-infection with Lyme disease or anaplasmosis. Patients with even mild to moderate illness may also have thrombocytopenia and anemia. Illness usually lasts weeks to months, occasionally with prolonged recovery lasting greater than a year with or without treatment. Symptoms in severe disease include acute respiratory failure, disseminated intravascular coagulopathy (DIC), congestive heart failure, acute liver and kidney 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. Reported mortality in moderate to severe cases varies from 5% to 35%. Diagnosis should be based upon epidemiologic risk factors and clinical evidence and confirmed by microscopic identification of the organism using Giemsa-stained thin blood smear and PCR. Approximately 1% to 10% of the RBCs are parasitized in immunocompetent hosts, but seldom exceeds 5%. In immunocompromised hosts, parasitemia up to 85% has been described.

Current management/treatment

Primary therapy for symptomatic infections is antibiotic combinations of atovaquone and azithromycin with or without quinine sulfate and clindamycin (reserved for moderate to severe cases). The duration of treatment is typically 7 to 10 days, but maybe extended in patients who are immunocompromised. Adjunctive RBC exchange can be considered for severely ill patients with parasitemia >10%, severe hemolytic anemia and/or severe lung, kidney, or liver compromise.

Rationale for therapeutic apheresis

RBC exchange may positively influence the course of severe babesiosis by correcting anemia, improving capillary perfusion and microcirculatory flow through the removal of infected RBC (reducing parasite load and modulating cytoadherence/microcirculation obstruction), as well as via the removal of cytokines produced by the hemolytic process (e.g., INF-α, TNF-α, IL-1, IL-6, nitric oxide, and thromboplastin substances) which can promote kidney failure and DIC. Questions remain as to the effect of RBC exchange on morbidity/mortality. A CS of 19 babesiosis patients receiving both antimicrobial therapy and adjunctive RBC exchange failed to identify a significant association between length of stay or mortality with post-procedural parasitemia levels (Nixon, 2019). This same author group also reported and compared this aforementioned cohort with 9 babesiosis patients receiving only antibiotic therapy, finding both groups required the same number of days to drop parasitemia <1%. The four reported fatal cases were within the RBC exchange group (Tannous, 2021). In severe cases, the benefits may outweigh the risks of the procedure, mainly exposure to multiple RBC transfusions and insertion of a central line. Post-procedural reduction of parasitemia levels has not been associated with decreased length of stay or mortality.

Technical notes

Automated apheresis instruments calculate the volume of RBCs required to achieve the desired post-procedure HCT, fraction of RBCs remaining and, by inference, the estimated final parasite load. A 2-volume RBC exchange can reduce the patient RBCs to roughly 10% to 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 to 2 total RBC volume(s) **Frequency:** Single procedure, but may be repeated if parasitemia >10%

Replacement fluid: Leukoreduced RBCs (or other as above)

Duration and discontinuation/number of procedures

The specific level of parasitemia to perform RBC exchange is unclear but >10% parasitemia in the presence of severe symptoms is the most commonly used guideline to initiate the procedure. The specific level to which parasitemia must be reduced to elicit the maximum therapeutic effect is also unknown, but a single RBC exchange can reduce parasitemia by 70% to 80%. Decision to repeat the exchange is based on the

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clinical condition (ongoing signs and symptoms) in the presence of post-exchange parasitemia (>10%). Treating physicians should be aware of the potential for rebound in parasitic burden post-RBC exchange and thus, post-exchange parasitemia surveillance is crucial.

Keywords: babesia, parasitemia, red blood cell exchange, erythrocytapheresis

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BURN SHOCK RESUSCITATION

Incidence: ~50,000 admissions for burn injuries/year

Procedure	Category		Grade	
TPE	III		2B	
# reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
	1 (17)	2 (66)	6 (102)	NA

Description

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, though colloid solutions may be included, typically starting 12 to 24 hours post-burn as part of salvage therapy. American and European guidelines indicate that the volume of crystalloid fluid resuscitation in the first 24 hours is typically 2-4 mL/kg body weight/%TBSA. Goals are to maintain urine output (UOP) while balancing risks of edema, ARDS, and organ hypoperfusion. Fluid resuscitation is successful in most patients. Patients with full-thickness burns, inhalation injury or resuscitation delay may have greater fluid requirements.

Rationale for therapeutic apheresis

The theoretical benefit of 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 capillary permeability and improve intravascular oncotic pressure, which might improve response to fluid resuscitation, mean arterial pressure (MAP), UOP, and immune function. In the only reported RCT of TPE in burn resuscitation, TPE did not alter the course of burn shock in 17 patients (9 TPE, 8 control arm) (Kravitz, 1989). However, the TPE group had significantly higher mean full-thickness burn injury and earlier completion of resuscitation. There were 3 deaths in the TPE group versus none in the control group. A retrospective CT of 40 patients found TPE increased MAP and UOP in the treated group and decreased the estimated intravascular fluid volumes required for resuscitation by 30% (Neff, 2010). Mortality was higher than predicted in both groups but was not statistically different between the two groups. However, the TPE-treated group had more severe burns, thus higher mortality would have been predicted. Finally, a trial looking at immunologic parameters in 26 patients with burns compared 13 patients who underwent TPE to those who had not with regard to a variety of immunologic markers (Stratta, 1986). No differences were seen except that serum from patients undergoing TPE had less suppression of the mixed lymphocyte reaction ($P<.10$). The TPE group had greater extent of burn injury and longer hospitalization but similar mortality to those patients who had not received TPE. Of the limited published CS, a variety of favorable physiologic effects were reported with respect to fluid resuscitation, UOP, heart function and immune benefits. Clinical outcome data were not consistently available. In one CS, TPE was applied in 5 clinical settings: failed fluid resuscitation, myoglobinuria, respiratory failure/ARDS, metabolic "exhaustion," and documented sepsis; however, the endpoint for clinical follow-up was not defined in this study (Ninnemann, 1984). Overall mortality with TPE was 32% without a control group for comparison, with 2 early deaths attributed to irreversible burn shock and 4 late deaths due to sepsis. A CS of 37 patients found statistically significant increased UOP and decreased crystalloid volume needed when comparing these parameters 3 hours before and 3 hours after TPE (Klein, 2009). 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 is instituted early in the post-burn period, typically 8 to 16 hours after injury. Patients treated with TPE typically have >20% to 50% TBSA burns and are refractory to fluid resuscitation in most reports. TPE has also been used at later time points in the management of thermal injury, for indications other than resuscitation. In one retrospective CT, TPE was initiated if the total resuscitation volumes exceeded 1.2X the volume predicted by the modified Baxter formula (3 mL Lactated Ringer's solution/kg actual body weight/%TBSA burn; Neff, 2010). Failure of conventional IV fluid resuscitation was defined as UOP <30 mL/hr and/or MAP <65 mmHg in the setting of increasing IV fluid volumes. The choice of replacement fluid is dependent on the indication for TPE, concomitant infection, and bleeding risk.

Volume treated: 1.5 TPV **Frequency:** See below

Replacement fluid: Albumin, plasma

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Duration and discontinuation/number of procedures

TPE is typically performed within the first 24 hours (8-16 hours) with additional 1 to 2 TPE procedures in selected patients whose MAP and UOP do not increase or whose IV fluid volumes do not decline to predicted volumes (second TPE within 6-8 hours of first). In several CS, patients were also included that received TPE at later time points, often for indications other than resuscitation.

Keywords: burn, shock, resuscitation, thermal injury, heat injury, plasma exchange

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CARDIAC NEONATAL LUPUS

Incidence: ~2% anti-SSA positive mothers

Procedure	Category		Grade	
TPE	III		2C	
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	5 (38)	14 (16)

Description

Congenital lupus can result in dermatologic, hematologic, hepatic, musculoskeletal, and central nervous system 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 passive transplacental transfer of maternal antibodies beginning at 12-weeks 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. CHB can result from the binding of the antibodies to fetal cardiac cells (undergoing physiologic apoptosis secondary to remodeling) resulting in autoimmune injury and fibrosis of the atrioventricular node and associated tissues. This predominately occurs between 18 and 24 weeks GA but can happen throughout the pregnancy. The antibodies may also block calcium channels within the myocardium resulting in inflammation and fibrosis, leading to endocardial fibroelastosis (EFE) and progression to heart failure, hydrops fetalis, and death. Two percent of mothers positive for anti-SSA and 1% of mothers with SLE have children with CHB. Recurrence rate in a mother with antibodies and a previously affected child is ~18%. Mothers may be asymptomatic (22%-40% asymptomatic; 50% develop autoimmune symptoms later), others may have systemic lupus erythematosus (SLE), Sjögren syndrome, antiphospholipid syndrome, or other autoimmune tissue disorders. Forty-one percent of neonates have at least one other affected sibling. Genetics and environment appear to play a role in disease manifestation; fraternal twins may not both demonstrate CHB. The incidence is higher in winter. With 2nd or 3rd degree AV block, 91% survive birth with 93% of the survivors living through the neonatal period; 2/3 of babies require a pacemaker by 1 year. Death is associated with earlier exposure to maternal autoantibodies (GA < 20 weeks), ventricular rate ≤50 bpm, fetal hydrops, and impaired left ventricular function. Fetal/neonatal mortality is higher with 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 with only electrocardiogram changes.

Current management

The current recommendation is for pregnant individuals with positive SSA ± SSB antibodies to have fetal cardiac evaluation every 2-3 weeks from 18 to 28 weeks GA to evaluate cardiac rhythm and function. Treatment is either prophylactic, when a mother has had a previously affected fetus/neonate, or symptomatic when CHB is detected in the current pregnancy. The mainstay of maternal treatment is fluorinated glucocorticoids and β-agonists; adjuvant therapies include TPE, IVIG, hydroxychloroquine, and other immunosuppressive agents. One study postulated that initiation of maternal hydrochloroquine (HCQ) therapy prior to 10-week GA in those with anti-SSA/SSB and a previously affected child may decrease CHB in the current pregnancy. The Preventive Approach to Congenital Heart Block with Hydroxychloroquine (PATCH) trial enrolled 54 Anti-SSA/Ro positive pregnant subjects with history of prior affected offspring; 400mg daily of HCQ was administered from gestational week 10 through delivery. This reduced the rate of CHB by more than 50% (Izmirly, 2020). IVIG has been found to lower titers of the causative antibody by 80% in select individuals. 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 to 24-week GA, which did not prevent recurrence (Friedman, 2010). Treatment of the mother for fetal reversal of 3rd degree CHB has not been achieved, but it has been stabilized. In some cases, 1st or 2nd degree CHB can be reverted to normal sinus rhythm. One case report detailed the course of an infant with CHB and dilated cardiomyopathy treated with multiple modalities including one plasmapheresis session (Rumancik, 2020).

Rationale for therapeutic apheresis

Removal of maternal antibodies by TPE may potentially prevent or reverse fetal/neonatal disease. Multiple CS and CRs have been published with varying success and regimens. TPE regimens varied from 3 procedures per week, weekly, every other week, to monthly. All patients received steroids and often received IVIG or azathriopine. In 3 patients with anti-SSA and mild fetal cardiac involvement who received IVIG, TPE, and steroids, fetal cardiac 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), described a regimen of TPE given 2 consecutive days then weekly until delivery, consisting of 70% to 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 during pregnancy 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 eversion of 2nd or 3rd degree) pregnancies. In pregnancies that responded, antibody titers fell long-term. A single CS of 4 patients using IA has been reported, which demonstrated prevention but not treatment of disease (Claus, 2006).

Technical notes

One case had small placental hemorrhage, which could have been due to anticoagulation during and after TPE. Apheresis of patients who are pregnant should always be performed with caution and multidisciplinary support.

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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.

Keywords: cardiac neonatal lupus, congenital heart block, anti-Ro (anti-SSA), anti-La (anti-SSB), anti-ribonuclear protein antigens, cardiomyopathy, plasma exchange, autoimmune, neonatal lupus erythematosus, Sjogren's syndrome

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CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

Incidence: ~5 cases per 10,000,000 persons per year; 584 patients in registry as of December 2021

Procedure	Category		Grade	
TPE	I		2C	
# reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
	0	0	8 (254)*	NA

*Includes registry data, which includes cases reported directly to the registry and/or published CRs and CS through December 2021 (López-Benjume, 2022) and additional subsequent published CS

Description

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 a lupus anticoagulant (LA) or persistent antiphospholipid antibodies such as anticardiolipin (aCL) and/or anti-β2-glycoprotein I (anti-β2GPI). Catastrophic APS (CAPS) is defined as the acute onset of multiple thromboses in at least 3 organ systems over a period of days or weeks, in patients with antiphospholipid antibodies. The sites most commonly affected 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 a complication in the clinical 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. As reported in the CAPS Registry, an international database of CAPS cases, in 2015, 65% of episodes were associated with precipitating factors, which preceded the clinical diagnosis of CAPS: infection was the most common finding, identified in 49% of the episodes, followed by surgery (17%), malignancy (16%), contraceptives (10%), pregnancy related (8%), and other (23%) (Rodríguez-Pintó, 2016). The presence of antiphospholipid antibodies among episodes of CAPS was LA 83%, aCL IgG 81%, aCL IgM 49%, anti-β2GPI IgG 78%, and anti-β2GPI IgM 40%. Other laboratory features of CAPS include thrombocytopenia (67%) and schistocytes on the peripheral blood smear (22%). The differential diagnosis includes sepsis, disseminated intravascular coagulation, heparin-induced thrombocytopenia, HELLP syndrome, thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome, and complications of systemic lupus erythematosus.

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 3 clear aims: treat any precipitating factors, prevent and control ongoing thrombosis, and suppress the excessive cytokine production. A triple therapy approach of anticoagulation plus corticosteroids plus TPE and/or IVIG is the recommended approach to therapy (Legault, 2018); however, combinations of these approaches and additional treatment strategies have been utilized. Based on the CAPS Registry cohort, this triple therapy approach was independently associated with higher survival among patients with CAPS. The mortality rates in patients treated with triple therapy, drugs included in the triple therapy but in other combinations, or none of the treatments included in the triple therapy were 29%, 41%, and 75% respectively (Rodríguez-Pintó, 2018). Mortality in patients who received triple therapy with both IVIG and TPE was similar to those that received triple therapy with either IVIG or TPE, thus it may not be necessary to administer both to patients. Several other therapeutic options have been tried in patients, particularly in refractory or relapsing cases, including cyclophosphamide, rituximab, and eculizumab.

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 may suggest plasma may not be always necessary in CAPS (Marson, 2008). Since plasma provides antithrombin, which is essential to mediate anticoagulation with heparin, the use of albumin alone as replacement fluid may prevent the beneficial effect of heparin anticoagulation, unless levels of antithrombin and heparin anticoagulation are 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 to 1.5 TPV **Frequency:** Daily or every other day

Replacement fluid: Plasma alone or in combination with albumin

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Duration and discontinuation/number of procedures

Most published cases have reported daily or every other day TPE for a minimum of 3 to 5 days up to courses of 1-3 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).

Keywords: catastrophic antiphospholipid syndrome, antiphospholipid syndrome, lupus anticoagulant, anticardiolipin antibodies, anti-β_2-glycoprotein I, plasma exchange, plasmapheresis, blood component removal, immunoadsorption

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CHRONIC ACQUIRED DEMYELINATING POLYNEUROPATHIES

Incidence: rare				
Indication	**Procedure**		**Category**	**Grade**
IgG/IgA/IgM related	TPE		I	1B
Anti-myelin-associated glycoprotein	TPE		III	1C
CANOMAD/CANDA	TPE		III	2C
# reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
IgG/IgA/IgM related	1 (39)	0	10 (136)	NA
Anti-myelin-associated glycoprotein*	0	0	3 (32)	1 (1)
CANOMAD/CANDA	0	0	2 (9)	10 (10)

CANOMAD= chronic ataxic neuropathy, ophthalmoplegia, immunoglobulin M paraprotein, cold agglutinins and disialosyl antibodies syndrome;
CANDA= chronic ataxic neuropathy with disialosyl antibodies syndrome;
*not inclusive, due to change of disease definition in later studies

Description

Coexistence of neuropathy and monoclonal gammopathy is a common clinical problem. Polyneuropathies are diverse in time of onset including acute, subacute, or chronic processes; sensory and/or motor neuropathic features; demyelinating and/or axonal electrophysiological features; and presence or absence of positive symptoms. Chronic acquired demyelinating polyneuropathies (CADP) include a variety of neuromuscular disorders resulting from immune-mediated demyelination including chronic inflammatory demyelinating polyradiculopathy (CIDP; see *separate fact sheet*) and atypical or less common variants of CIDP, multifocal motor neuropathy (MMN), IgG/IgA/IgM paraproteinemic polyneuropathy, neuropathy associated with IgM antibodies to myelin-associated glycoprotein (anti-MAG), POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), chronic ataxic neuropathies due to disialosyl antibodies, and other neuropathic syndromes associated with monoclonal gammopathy. POEMS is a category IV indication described in the JCA 2013 Special Edition and MMN is a category IV indication described in the JCA 2019 Special Edition.

The classification of CADP takes into consideration both disease presentation and pathological etiology. The diagnostic algorithm includes detailed neurologic examination; nerve conduction studies, which may show demyelinating, axonal, or equivocal/mixed patterns; hematology (complete blood count) panel; cerebrospinal fluid analysis; serum and urine protein electrophoresis with immunofixation; and testing for anti-MAG and anti-ganglioside antibodies. Some patients may require nerve biopsy. For patients with sensorimotor neuropathy, after confirmation of demyelination, further classification is based on antibody specificity.

The detection of anti-MAG antibodies in the setting of IgM monoclonal gammopathy associated neuropathy establishes the diagnosis of anti-MAG neuropathy. The typical presentation of anti-MAG neuropathy is a predominantly sensory ataxic symmetric demyelinating distal neuropathy starting in the legs, with gait disturbance and tremor in the arms as the predominant disabling symptoms. 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% to 35% of cases, it is associated with Waldenström macroglobulinemia (WM) or B cell lymphoma. Anti-MAG antibodies and paraproteinemia are frequently detected in patients with distal acquired demyelinating symmetric neuropathy (DADS). DADS without anti-MAG is considered a CIDP variant and treated similar to CIDP, while DADS with anti-MAG (like other IgM-associated neuropathies) often has a worse response to therapy than classical CIDP.

The chronic ataxic neuropathies associated with disialosyl antibodies includes CANOMAD and the less restrictively defined CANDA. CANOMAD/CANDA is associated with antibodies directed against the gangliosides containing disialosyl groups including GQ1b, GD1b, GT1b, and GD3. The course of CANOMAD/CANDA is usually relapsing and remitting. Overt malignancies are found in 36% of patients, with WM the most frequent (Le Cann, 2020). Both demyelinating and axonal patterns may be seen.

The prevalence of neuropathy in MGUS ranges from 8% to 36% and is higher in patients with IgM than with IgG or IgA MGUS (Nobile-Orazio, 2017). Evidence suggests patients with chronic demyelinating neuropathy associated with IgG or IgA MGUS should be treated similar to patients with idiopathic CIDP (Stork, 2015). Patients with multiple myeloma may have neuropathy at presentation or develop it later in their disease course and may be due a variety of mechanisms (Mohyuddin, 2017).

Current management/treatment

The optimal treatment regimen is not clear. Response to immunosuppressive drugs varies. A large meta-analysis suggests limited support for the use of TPE, cyclophosphamide combined with prednisolone, IVIG, and corticosteroids for IgG and IgA paraproteinemic neuropathies (Stork, 2015). Based on a meta-analysis of IgM anti-MAG paraprotein-associated peripheral neuropathies, there is inadequate reliable evidence from trials of immunotherapies in support of any particular treatment (Lunn, 2016); however, analysis of two RCT on rituximab provide low quality evidence of benefit (Dalakas, 2009; Léger, 2013). While IVIG and rituximab are the most frequent treatments, other immunosuppressive therapies have been used as well. Clinical improvement is often seen when there is at least a 50% reduction of serum IgM.

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Rationale for therapeutic apheresis

The rationale for using TPE is to remove anti-MAG or other antibodies; however, not all patients respond and the response may be short lived. TPE may be more effective for IgA and IgG MGUS-associated polyneuropathy, than for IgM-MGUS (Cortese, 2011). TPE may result in a transient response in anti-MAG neuropathy. In one report of 19 patients with anti-MAG neuropathy who received TPE, 40% had a transient effect, but most of them had a relapse upon stopping TPE (Gorson, 2001). For CANOMAD/CANDA, retrospective studies suggest benefit in 40 to 50% treated with TPE/DFPP; however, the largest study of 45 patients suggests IVIG and rituximab are the most effective therapies (Le Cann, 2020). Currently, other treatments are considered first-line for anti-MAG neuropathy.

Technical notes

Volume treated: 1 to 1.5 TPV **Frequency:** See below

Replacement fluid: Albumin

Duration and discontinuation/number of procedures

Typical course is 3 to 6 treatments over 10 to 14 days with regimen being guided by clinical symptomatology.

Keywords: paraproteinemic polyneuropathy, neuropathy, polyneuropathy, paraproteinemic demyelinating neuropathies, chronic acquired demyelinating polyneuropathies, plasma exchange.

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CHRONIC FOCAL ENCEPHALITIS

Incidence: ~2/10,000,000 under age 18 years

Procedure	Category		Grade	
TPE/IA	III		2C	
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	3 (10)	10 (13)

Description

Chronic focal encephalitis (CFE), also known as Rasmussen encephalitis (RE), is a rare, inflammatory, and possibly immune mediated disease characterized by unilateral inflammation of the cerebral cortex. The two cardinal symptoms are progressive neurological deficits and intractable focal seizures, often in the form of epilepsia partialis continua and recurring status epilepticus. Distinctive magnetic resonance imaging (MRI) features include progressive unilateral focal cortical atrophy, usually in the frontal lobe or the insula. Onset is typically in childhood (mean age 6 years). A similar syndrome has also been described in adults (~10% of cases). Adult onset presentations are characterized by a slower clinical course and less severe neurologic deficits. The etiology of CFE is unknown, but antecedent infections have been implicated, including Epstein-Barr virus, herpes simplex virus 6, or cytomegalovirus. Diagnosis can be made using the European consensus statement criteria, which is based on clinical, electrophysiological, neuroimaging, and morphological characteristics (Bien, 2005). Histopathologic features show microglial and lymphocytic nodules with perivascular cuffing, neuronal death, and neurophagia progressing to cortical cavitation, astrogliosis, and neural loss. These findings suggest both immune mediation of adaptive immunity via T lymphocyte responses and innate immunity characterized by microglia and astroglia. Since no specific electroencephalogram (EEG) abnormalities can distinguish CFE from other types of focal epilepsy, MRI of the brain is the mainstay for diagnostic assessment and follow-up.

Current management/treatment

Treatment aims to reduce seizure activity and frequency and improve functional long-term outcome, as measured by both motor and cognitive performance. Anticonvulsants are necessary but not always effective, nor do they arrest progression. Thus, treatment should be adjusted to optimize seizure control and minimize side effects. Surgery (functional or anatomical hemispherectomy) is the only definite treatment for controlling seizures. However, surgery can lead to complications such as comprehending homonymous hemianopia, hemiplegia, or aphasia. Immunotherapy can slow disease progression, but does not halt or cure the disease and thus, may be used in early stages of the disease or in patients with slow disease progression, with mild deficits, and/or not suitable for surgery (Lagarde, 2022). 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 given prior to a trial of steroids in patients with established disease and may modestly improve hemiparesis. Intraventricular interferon-α, intravenous rituximab, azathioprine, mycophenolate mofetil, and tacrolimus have been investigated for control of epileptic and neurological aspects of CFE. In a CR, use of natalizumab was reported to decrease seizure frequency (Bittner, 2013). In a small group of patients, adalimumab had good seizure control efficacy and decreased functional decline (Lagarde, 2016). Ganciclovir has been also used and showed some therapeutic effect in patients treated early after symptom appearance (1-3 months). Given that the severity of symptoms varies among different patients and phases, the therapeutic strategy, including medical and surgical options, must be individualized.

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. However, there is no consistent association with specific autoantibodies in plasma or cerebrospinal fluid. The demonstration of serum immunoreactivity to the glutamate receptor GluR3 in three individuals with histologically confirmed CFE led to the use of TPE in a 9-year-old (Rogers, 1994). Seven TPE procedures performed 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 the patient deteriorated clinically but had transient responses to a repeat course of therapy. Other reports indicate that serum GluR3 immunoreactivity, which was found in only a few patients with CFE, is a feature of epilepsy syndromes and not specific to CFE. However, other brain autoantibodies have also been identified in patients with CFE, including anti-GluR3B and other anti-neuronal antibodies (e.g., Munc-18 and alpha7-acetylcholine receptor). Clinical and EEG parameters of epileptogenesis were transiently diminished by TPE in two patients. Monthly courses of IA using a staphylococcal protein A column diminished seizure frequency and halted cognitive deterioration over a 2-year period in a 16-year-old with IgG anti-GluR3 antibodies and controlled status epilepticus in a 20-year-old (Antozzi, 1998). Despite the paucity of reports, a concerted trial of immunotherapy, including apheresis, to control seizures, mitigate functional decline, and delay the need for hemispherectomy in patients with CFE 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. Use of TPE or IA is limited to few cases.

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Volume treated: TPE: 1 to 1.5 TPV; IA: up to 2.5 TPV

Replacement fluid: TPE: albumin; IA: NA

Frequency: Initial course of 5 to 7 TPE or IA, adjusted to the individual response and concomitant immunosuppressive treatment

Duration and discontinuation/number of procedures

After an initial course of treatment, subsequent courses of TPE (with or without IVIG), or IA may be performed at intervals of 1 to several weeks for a period up to 9 months as empirically needed to maintain clinical stability and avoid or delay hemispherectomy. Immunosuppressive medications may increase the interval between courses.

Keywords: chronic focal encephalitis, Rasmussen encephalitis

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CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

Prevalence: 1 to 10/100,000				
Procedure	**Category**		**Grade**	
TPE/IA	I		1B	
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
TPE	4 (99)	0	>10 (>200)	NA
IA	3 (65)	0	2 (44)	NA

Description

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired autoimmune neuropathy affecting the peripheral nerves and nerve roots. CIDP occurs mainly in adults and is a heterogenous group of disorders. The typical form of CIDP accounts for ~50% to 60% of cases and is a symmetric sensorimotor polyneuropathy (motor involvement is usually greater than sensory). Autonomic involvement is usually mild and limited. The disease typically develops gradually over several months and may have a chronic progressive or relapsing course. Atypical CIDP variants have been described including Lewis-Sumner syndrome (multifocal acquired demyelinating sensory and motor neuropathy, MADSAM), distal acquired demyelinating (DADS) neuropathy, purely motor, purely sensory, and focal CIDP. CIDP can occur in conjunction with other disorders such as HIV and diabetes. It can be difficult to distinguish acute-onset CIDP from acute inflammatory demyelinating polyneuropathy (AIDP; see *separate fact sheet*). Other chronic neuropathies such as multifocal motor neuropathy and neuropathy associated with an IgM monoclonal gammopathy can also mimic CIDP (see Chronic acquired demyelinating polyneuropathies). Similar clinical presentations may be seen with inherited paraneoplastic and toxic neuropathies and neuropathies associated with nutritional deficiency, porphyria, or critical illness. Diagnosis is usually made on clinical presentation using the criteria proposed by the European Federation of Neurological Societies and the Peripheral Nerve Society [EFNS/PNS] and confirmed by electrodiagnostic findings. There is no laboratory test finding that is specific to CIDP; however, laboratory tests are used to look for diseases that mimic or are associated with CIDP.

Current management/treatment

Therapy should be initiated early to stop the inflammatory demyelination and prevent secondary axonal degeneration and permanent disability. There are 3 first-line initial treatment options with similar efficacy: steroids, IVIG, or TPE (Van den Bergh, 2021). The initial treatment is often based on ease of administration, cost, availability, and/or side effects. Possibly due to the heterogeneity of CIDP, individuals may differ in response to any one of these modalities. Specifically, IVIG may not be as effective in IgG4 subtype nodopathies (e.g., neurofascin-155 and contactin-1 or contactin-associated protein 1 antibody). Therapeutic response provides guidance as to when treatment can be tapered or discontinued and is measured by objective improvement, such as quantitative grip measure or results of a disability scale. About two-third of patients will respond to any single first-line initial therapy and thus, correct diagnoses must be considered for patients who are refractory to more than one first-line treatment. Furthermore, approximately 30% of patients will achieve remission and thus, maintenance therapy is required in the majority of patients, including steroids, IVIG, subcutaneous immune globulin, and/or periodic TPE. Frequency and dosage of maintenance therapy is guided by the patient's symptoms and treatment response. Secondary therapies can be used in patients who fail initial therapy, are refractory to treatment, or to reduce long-term steroid dose, including azathioprine, cyclophosphamide, cyclosporin, mycophenolate mofetil, rituximab, and autologous hematopoietic progenitor cell transplantation.

Rationale for therapeutic apheresis

The presumed etiology of CIDP is autoimmune attack on the peripheral nerves with both humoral and cell-mediated immunity implicated. For example, increased serum inflammatory cytokines, activated circulating T lymphocytes, and the presence of CD4/CD8 cells in nerve biopsy samples suggest that T cells play an important role. B cell phenotypes are also altered in CIDP and immunoglobulin and complement deposition are seen on nerve fibers. In approximately 10% of patients, autoantibodies against nodal and paranodal proteins (such as neurofascin 155, neurofascin 140, neurofascin 186, contactin 1, and contactin-associated protein 1) are identified. These patients may have a different presentation from those with classic CIDP. Nevertheless, disease classification is evolving.

TPE or IA can remove antibodies, immunoglobulins, cytokines, and complement. In the first double-blind, sham-RCT, patients who received TPE (average 47 mL/kg of plasma exchanged) versus sham procedures twice weekly for 3 weeks demonstrated significant improvement in nerve conduction measurements (Dyck, 1986). In a different randomized double-blind crossover trial, patients received 10 TPE (40-50 mL/kg plasma exchanged) or sham procedures over 4 weeks had substantial improvement in their neurological function. Many, however, relapsed within 1 to 2 weeks, but responded to continued TPE (Hahn, 1996). In another randomized crossover trial of TPE (twice a week for 3 weeks then once a week for 3 weeks) versus IVIG (0.4 gm/kg once a week for 3 weeks then 0.2 gm/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 (Dyck, 1994).

In a randomized pilot trial of TPE versus IA, patients received each 6 treatments with an equal plasma volume of 2.5L per treatment. Both TPE and IA resulted in substantial clinical improvement in 44% versus 67% of patients (Lieker, 2017). Another RCT demonstrated comparable treatment response and safety between TPE and IA in patients with neurological autoimmune diseases (Boedecker, 2022).

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Technical notes

Volume treated: 1 to 1.5 TPV

Frequency: 2 to 3/week until improvement, then tapered, e.g., weekly or monthly

Replacement fluid: TPE: albumin; IA: NA

Duration and discontinuation/number of procedures

TPE or IA is safe and effective in providing short-term benefit, but rapid deterioration may occur afterwards. This may necessitate maintenance treatment, with repeated TPE, IA and/or other immunomodulating therapies, with frequency tailored to symptoms and tolerability of the individual patient.

Keywords: chronic inflammatory demyelinating polyradiculoneuropathy, demyelinating neuropathy, plasma exchange, immunoadsorption

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COAGULATION FACTOR DEFICIENCY AND INHIBITORS

Incidence: Factor VIII inhibitor: <2/1,000,000/year; inhibitors to other coagulation factors: rare

Procedure	Category		Grade	
IA	III		2B	
TPE	III		2C	
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
IA	0	0	12 (132)	NA
TPE	0	0	10 (104)	NA

Description

Coagulation factor inhibitors (antibodies) target specific coagulation factors leading to factor deficiency and potentially hemorrhage. Patients with moderate to severe congenital factor VIII or IX (FVIII or FIX) deficiency (hemophilia A and B, respectively) may make alloantibodies to exogenous factor replacement. This serious complication occurs in 20% to 30% and 3% to 5% of patients with hemophilia A and B, respectively. Congenital factor XI deficiency (hemophilia C, thromboplastin antecedent [PTA] deficiency, Rosenthal syndrome) is a rare (1:1,000,000) hemostatic disorder that is generally mild without spontaneous bleeding, but can cause severe bleeding in trauma or during surgical procedures.

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). FVIII autoantibody development has a biphasic age distribution (small peak in childbearing years due to post-partum inhibitors and major peak in the elderly) with only approximately half of cases associated with a concomitant disease (e.g., pregnancy, malignancy, autoimmune disorder, infection, and medications). In acquired FVIII deficiency, hemorrhage tends to affect skin, muscle, soft tissue, and mucous membranes, rather than hemarthroses. Cross reactive xenotropic 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 (LAC) 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 VWF function. 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). Systemic light chain amyloidosis is associated with acquired factor deficiency, most commonly FX, due to selective binding of coagulation factors to amyloid fibrils. In the case of FX deficiency laboratory measurements of coagulation function and FX activity levels are poor predictors of bleeding risk. Rare cases of inhibitors have also been reported for other coagulation factors, including FVII, FIX, FXI, FXIII, and protein S. Acquired protein S deficiency has been reported in some patients with varicella-associated purpura fulminans.

The bleeding tendency with factor inhibitors is due to clearance of the specific factor and/or direct inhibition of 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 acquired hemophilia A include high doses of FVIII, modified FVIII products, and FVIII bypassing factors, such as activated prothrombin complex concentrates (PCC) and recombinant factor VIIa (rFVIIa). Treatment for suppression of inhibitor production may include several modalities. Based on European Acquired Haemophilia Registry (EACH2) data, approximately 70% of patients with acquired hemophilia A achieved complete remission with steroids plus cyclophosphamide (Collins, 2012). Treatment of patients with acquired FVIII inhibitors using the modified Bonn-Malmö protocol (IA, IVIG, cyclophosphamide, prednisolone, and FVIII), resulted in a 93% complete remission rate in the first year in patients without paraneoplastic syndromes (Zeitler, 2012). In congenital hemophilia A, immunologic tolerance can be induced by daily infusions of FVIII. Patients with acquired FV inhibitors have been treated with immunosuppression, IVIG and platelet and/or plasma transfusion. Patients with AVWS and hemorrhage are usually managed with desmopressin, antifibrinolytics, von Willebrand factor replacement therapy, activated PCC, IVIG or rFVIIa. Hypoprothrombinemia associated with LAC is treated with PCC and corticosteroids. MPN and plasma cell dyscrasias are treated as above to control bleeding, as well as treating the underlying disorder. Patients with congenital FXI deficiency or acquired FXI inhibitors are treated with plasma transfusion and/or FXI concentrates (not available in the United States). Immunosuppression is used in patients with acquired inhibitors.

Rationale for therapeutic apheresis

The extracorporeal removal of coagulation factor inhibitors with IA is better studied than TPE. CS and CRs indicate 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.

TPE has been used to reduce inhibitor levels in patients with inhibitors to FVIII and several other coagulation factor inhibitors. Similar to IA, not all patients have responded to this therapy. CRs have conflicting results on the use of TPE in patients with systemic amyloidosis associated factor deficiency. Small CS and CRs also describe the use of TPE to increase factor levels in patients without an inhibitor when a specific factor replacement product was unavailable or when the volume of simple plasma transfusion needed to reach target levels was greater than the patient would tolerate. For example, FXI concentrates are not available in the US and the amount of plasma transfusion needed to raise FXI levels to 50 IU/dL can be as high as 3000 mL (Burgos Pratx, 2021).

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Technical notes

IA is a two-step procedure with plasma separation followed by plasma adsorption using plasma flow rates according to manufacturers' recommendations, generally in the range of 30 to 40 mL/min. Regenerative IA systems may be preferred in this patient group. Anticoagulant should be used at the lowest required amount.

Volume treated: TPE: 1 to 1.5 TPV; IA:2 to 3 TPV **Frequency:** TPE, IA: Daily

Replacement fluid: TPE: plasma; IA: NA

Duration and discontinuation/number of procedures

Treatments are performed daily until bleeding is controlled with other therapeutic modalities.

Keywords: hemophilia, factor inhibitor, plasma exchange, immunoadsorption

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COMPLEX REGIONAL PAIN SYNDROME

Incidence: 5-26/100,000/year

Indication	Procedure		Category	Grade
Chronic	TPE		III	2C
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	3 (45)	2 (3)

Description

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. There are two subtypes—type I and type II. While type I is more common (~90% of patients) and does not involve peripheral nerve injury, type II shows evidence of peripheral nerve injury. Patients with CRPS typically present with debilitating pain and prominent autonomic and inflammatory changes, 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), and genitourinary (urinary retention), as well as generalized symptoms, like weakness and fatigue.

CRPS may be preceded by a traumatic event, such as fracture, soft tissue injury, or surgery. Nonetheless, up to 10% of patients have no inciting event identified. Although the majority of CRPS will resolve within weeks to months (acute CRPS), some may persist beyond one year in duration and become chronic. CRPS has been associated with HLA-DQ8 or HLA-B62. CRPS may also occur in children, in whom lower extremity involvement and systemic dysautonomia have been reported. The pathophysiological mechanisms of CRPS are complex and not fully understood; however, increases in proinflammatory cytokines and decreases in anti-inflammatory proteins have been observed. CRPS has also been associated with autoantibodies against β2-adrenergic, α1-adrenergic, and muscarinic M2 receptors. Peripheral sensitization resulting in increased synaptic transmission in the spinal cord may also be involved in the pathogenesis. Differential diagnoses include autoimmune dysautonia (see *separate fact sheet*), infection, compartment syndrome, erythromelalgia, and peripheral neuropathy. Currently, there are no laboratory tests that can be used for definitive diagnosis. Although the Budapest consensus criteria (Harden, 2010) are useful in the clinical setting, CRPS remains a diagnosis of exclusion.

Current management/treatment

Chronic or severe CRPS is challenging to manage. Multidisciplinary approaches are generally used and recommended to achieve the goal of decreasing pain and restoring function in affected limbs (Harden, 2022). Referral to a pain specialist may be necessary. Physical and occupational therapy along with behavioral management are used as part of the multidisciplinary approach. Many therapeutic agents have been used with variable and often partial efficacy including bisphosphonates, gabapentin, calcitonin, intravenous ketamine, free radical scavengers, oral corticosteroids, and spinal cord stimulation. Due to the suspected autoimmune nature of the disease (in at least a subset of patients), steroids, IVIG, and rituximab have been tried. Notably, low dose IVIG for 6 weeks was not effective compared to placebo in alleviating pain in patients with moderate to severe CRPS of 1 to 5 years duration in a randomized trial (Goebel, 2017). Nonetheless, corticosteroids may be useful (van den Berg, 2022). Other therapies include spinal cord stimulation, dorsal root ganglia stimulation, epidural clonidine, and sympathectomy. Review of the published literature on the use of TPE in CRPS suggests that the majority of patients with CRPS (41/45) who underwent TPE (5-7 TPEs over 2-3 weeks) reported positive responses in terms of pain or improvement of other systemic symptoms. The majority required ongoing maintenance TPE and/or immunosuppressive medications and adjunctive therapies to maintain symptomatic improvement.

Rationale for therapeutic apheresis

TPE can remove autoantibodies to ß2-adrenergic, α1-adrenergic, and muscarinic M2 receptors (and possibly cytokines), and may relieve localized and systemic symptoms thorough this mechanism. The effect is likely transient. Maintenance TPE may be required, in combination with other therapies.

Technical notes

Volume treated: 1 to 1.5 TPV

Frequency: 5 to 7 TPEs over a 2 to 3 week period

Replacement fluid: Albumin

Duration and discontinuation/number of procedures

As above, and then as indicated for maintenance management (as frequent as weekly).

Keywords: complex regional pain syndrome, plasma exchange

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CRYOGLOBULINEMIA

Incidence: ~50% of patients with chronic hepatitis C virus

Indication	Procedure		Category	Grade
Severe/symptomatic	TPE/DFPP		II	2A
	IA		II	2B
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
TPE	1 (59)	0	>10 (>200)	NA
IA	1 (17)	0	1 (4)	0

Description

Cryoglobulins are immunoglobulins that reversibly precipitate below body temperature. Patients with cryoglobulinemia may be asymptomatic or they may present with arthralgia, purpura, skin ulcers, glomerulonephritis, peripheral neuropathy and systemic vasculitis. Purpura and ulceration most commonly occur on the skin of lower extremities because of exposure to lower temperatures. Cryoglobulinemia is associated with a wide variety of diseases including lymphoproliferative disorders, autoimmune disorders, and viral infections (e.g., hepatitis B virus (HBV) and hepatitis C virus (HCV)). Cryoglobulins may cause hyperviscosity, and the aggregates of cryoglobulins can deposit on endothelial surfaces of small-to-medium vessels and cause a systemic inflammatory syndrome including activation of complement and leukocyte recruitment. When cryoglobulinemic vasculitis is present, the disease is referred to as CryoVas. Cryoglobulins are classified into three types based on their immunoglobulin (Ig) subgroup: type I consists of monoclonal Igs, usually due to multiple myeloma (IgG) or Waldenström's macroglobulinemia (IgM); type II contains polyclonal IgG, monoclonal IgM (or IgG or IgA) and rheumatoid factor, usually due to HCV infection; and type III contains polyclonal IgG and polyclonal IgM and are usually due to inflammatory disorders, autoimmune disease, or HCV infection. About 80% to 90% of individuals with mixed cryoglobulinemia (MC) (types II and III) have HCV; the remaining 10% to 20% of MC are secondary to other viral infections (HBV and human immunodeficiency virus [HIV] being the most common), systemic autoimmune diseases, or chronic lymphoproliferative disorders. 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, however response to TPE has been shown to be aligned with a measurable decrease in cryocrit. Individuals with type I tend to have a higher cryocrit than individuals with type II or III.

Current management/treatment

Management is based on the severity of symptoms and treating the underlying disorder. Screening for infectious and autoimmune disorders 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 targeting the underlying associated disorder as well as the use of immunosuppressive therapy such as corticosteroids, cyclophosphamide, and rituximab. In a multicenter RCT, rituximab (1g IV at baseline and day 14) was compared with conventional treatment (corticosteroids plus azathioprine, cyclophosphamide, or TPE) in 59 patients with severe mixed CryoVas (De Vita, 2012). Survival at 12 months was statistically higher in the rituximab group compared with conventional therapy (64% vs. 4%, respectively). A large CS (CryoVas survey) demonstrated greatest therapeutic efficacy of rituximab plus corticosteroids over corticosteroids alone or with alkylating agents in patients with noninfectious mixed CryoVas (Terrier, 2012, 2015). A separate RCT in patients with severe HCV-associated CryoVas demonstrated significantly greater remission rates in patients in the rituximab group compared with conventional therapy (83% vs. 8%, respectfully; $P<.001$) (Sneller, 2012). HCV RNA levels were not affected by rituximab therapy. Over the last several years, interferon-free regimens that employ potent direct-acting antiviral (DAA) agents have demonstrated high virological responses and appear safer than interferon-containing regimens; however, immunological and clinical responses may be less satisfactory and second line treatment with rituximab may still be needed. Some patients with life-threatening disease or cryoglobulinemia-associated hyperviscosity syndrome may benefit from adjunctive TPE to control the symptoms by directly removing the cryoglobulins.

Rationale for therapeutic apheresis

TPE removes cryoglobulins efficiently, with CRs and CS suggesting improvement in 70% to 80% of treated patients. It has been used primarily in active moderate-to-severe cryoglobulinemia with kidney function impairment (frequently membranoproliferative glomerulonephritis), peripheral 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 of this condition. In one multicenter CS, 13% of 913 patients with HCV-CryoVas treated with DAA experienced CryoVas relapse which were treated with corticosteroids in 91% of cases, TPE (50%), cyclophosphamide (37%), or rituximab (6%) (Fayed, 2022).

Double (or cascade) filtration plasmapheresis (DFPP), 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. In the largest retrospective cohort study of 159 patients with CryoVas, TPE and cascade filtration were confirmed to be safe procedures and overall demonstrated response in 77% of patients, with good or very good response in 52% (Marson, 2018). A further conclusion was that apheresis should be considered early in the disease course especially in cases with impending kidney involvement, to prevent irreversible kidney damage, and should be considered an emergency treatment.

Another less frequent apheresis modality used in this disease is cryofiltration which cools the plasma in an extracorporeal circuit, either continuously or in a 2-step procedure to remove cryoglobulins; the remaining plasma is warmed to body temperature prior to returning to the patient. Cryofiltration is less efficient at removing cryoglobulins than DFPP. In a randomized, parallel-group study, IA apheresis was shown to be effective in lowering cryoglobulins in HCV-related cryoglobulinemia (Stefanutti, 2009).

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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 to 1.5 TPV **Frequency:** Every 1 to 3 days

Replacement fluid: Albumin

Duration and discontinuation/number of procedures

For acute symptoms, performance of 3 to 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.

Keywords: cryoglobulinemia, CryoVas, cryocrit, vasculitis, HCV, cryofiltration, immunoadsorption, plasma exchange

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CUTANEOUS T CELL LYMPHOMA

Incidence: mycosis fungoides: 6/1,000,000/year; Sézary syndrome: 1/1,000,000/year

Indication	Procedure		Category	Grade
Erythrodermic	ECP		I	1B
Non-erythrodermic	ECP		III	2B
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Erythrodermic	0	4 (64)	>10 (>200)*	NA
Non-erythrodermic	1 (8)	2 (18)	15 (114)	NA

*Includes mixed erythrodermic/non-erythrodermic cases.

Description

Mycosis fungoides (MF) and its leukemic variant, Sézary syndrome (SS), account for 55% and 5% of cutaneous T cell lymphoma (CTCL) cases, respectively. Although both involve clonal (malignant) epidermotropic CD3+/CD4+ T cells, molecular studies and immunophenotypic analyses suggest that MF and SS evolve from different cells of origin. Diagnosis incorporates clinical, histopathologic, molecular and immunopathologic criteria. Disease staging evaluates skin, lymph node, visceral and blood involvement using TNMB criteria. Early stage MF (stage IA, IB, and IIA) can be challenging to diagnose. Stage I disease is limited to the skin with patches, papules or plaques (IA < 10% body surface area [BSA]; IB ≥ 10%). Stage II indicates low grade lymph node involvement (IIA) or skin tumors (IIB). Erythrodermic MF is characterized by generalized erythroderma (≥80% BSA) alone (IIIA) or in the presence of a low burden (< 5%) of clonal CD4+ T cells (Sézary cells) in the peripheral blood (IIIB). SS specifically denotes generalized erythroderma with nodal involvement and a high burden ($\geq 1 \times 10^9$/L) of circulating Sézary cells (IVA1). Disease with high-grade lymph node (IVA2) or visceral involvement (IVB) is associated with a very poor prognosis.

Current management/treatment

The treatment of MF/SS is usually palliative with therapy aimed at alleviating symptoms, improving skin manifestations, controlling extracutaneous complications and minimizing immunosuppression. Current skin directed treatment options include topical corticosteroids, topical mechlorethamine, topical bexarotene, ultraviolet phototherapy (PUVA or UVB), local radiotherapy and total skin electron beam therapy. Systemic therapies include retinoids (bexarotene, all-trans retinoic acid), interferon-alpha, chemotherapy (methotrexate, pralatrexate, liposomal doxorubicin, gemcitabine), monoclonal antibodies (alemtuzumab, brentuximab, mogamulizumab), ECP, histone deacetylase inhibitors (vorinostat, romidepsin), and allogeneic stem cell transplantation Treatment recommendations are based on stage (Trautinger, 2017). For advanced CTCL, a multimodality approach with the use of additional therapies or "layering on" of therapies is often preferred. New immunotherapeutic therapies, such as IL-12, TLR-agonists, checkpoint inhibitors and CAR-T, have displayed promise in clinical trials or are in development. ECP is currently recommended as first line treatment, either alone or in combination with other skin directed or systemic therapies, for treatment of stage IIIA, IIIB and IVA1/SS disease and for maintenance after remission has been achieved. A study of patients with CTCL receiving systemic treatment demonstrated that 1 in 10 patients were on ECP therapy (Ling, 2020).

Rationale for therapeutic apheresis

ECP involves leukapheresis, ex vivo treatment with 8-methoxypsoralen and UVA light, and subsequent reinfusion of the treated cells. Treatment induces apoptosis of malignant cells, which are phagocytosed by antigen presenting cells following reinfusion, and stimulates monocyte differentiation to myeloid dendritic cells with a Th1 phenotype that launch a cytotoxic response against the malignant clone. The overall response rate of CTCL to ECP is approximately 60% with complete response rates of 14% to 26%. Response to ECP correlates with short duration of disease, early use of ECP in the treatment paradigm, lower blood Sézary cell burden and significant early response of skin lesions (i.e., >50% regression within 6 months). ECP can be combined with systemic therapy such as retinoids, interferons and mogamulizumab for better response. ECP is not currently recommended for non-erythrodermic disease as it is thought to require blood involvement to be effective. However, there are CRs suggesting effectiveness and the National Comprehensive Cancer Network Guidelines lists ECP as a treatment option for refractory early stage disease. There has only been one small RCT comparing PUVA and ECP in the treatment of plaque stage (T2) MF (Child, 2004). However, there are no prospective, placebo-controlled, RCTs that evaluate the impact of ECP treatment on survival and comparisons are usually made with historical controls. Advantages of ECP include the relative lack of immune suppression and lower risk of infections compared to systemic therapy.

Technical notes

One cycle (two 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. Several of the earlier studies in CTCL were performed using ECP on two consecutive days, many centers still choose to treat in this manner. Iron deficiency anemia has been documented in patients with CTCL undergoing ECP; for long-term management, patients should be evaluated and monitored periodically for iron status.

Volume treated: Varies

Frequency: Two days (one cycle) every 2 to 4 weeks, benefit is not seen with more frequent treatments

Replacement fluid: NA

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Duration and discontinuation/number of procedures

The median time for a maximal response to ECP is 5 to 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 in skin, blood and lymph nodes documented as per published guidelines. When maximal response is achieved with ECP, it can be reduced to one cycle every 6 to 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.

Keywords: cutaneous T-cell lymphoma, Sezary syndrome, mycosis fungoides, extracorporeal photochemotherapy

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DILATED CARDIOMYOPATHY, IDIOPATHIC

Incidence: ~36/100,000/year (Europe and North America)

Indication	Procedure		Category	Grade
NYHA functional classification II-IV	IA		II	1B
	TPE		III	2C
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
IA	4 (109)	12 (499)	NA	NA
TPE	0	0	3 (21)	3 (3)

NYHA = New York Heart Association.

Description

Dilated cardiomyopathy (DCM) is characterized by progressive left ventricular or biventricular dysfunction and dilation that are not explained by abnormal loading conditions or coronary artery disease. Clinically patients present with signs and symptoms of congestive heart failure (dyspnea, orthopnea, impaired exercise tolerance, fatigue, and peripheral edema) and arrhythmias. There are several etiologies of DCM including genetic, infection, systemic immune-mediated disease, toxic and overload, drugs, endocrine/metabolic, and peripartum. Fifty percent of cases are idiopathic (iDCM). A genetic determinant is present in up to 40% to 50% of patients with DCM, with truncation variants of the titin gene (*TTN*tv) the most common (Tharp, 2019). The pathogenesis of the remaining iDCM cases appears to involve autoimmunity often 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 [β1AR], Troponin-I, Na-K-ATPase, M2-muscarinic acetylcholine receptor).

Current management/treatment

DCM is usually managed with guideline directed medical therapy for heart failure that includes angiotensin converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor-neprilysin inhibitors, β-blockers, mineralocorticoid receptor antagonists, placement of an implantable cardioverter-defibrillator (ICD), and treatment of underlying disease and risk factors (e.g., diabetes, hyperlipidemia). Surgical management includes placement of a left ventricular assist device (LVAD) with the definitive therapy being heart transplantation. DCM is the most common indication for heart transplantation in adult and pediatric patients. Treatment of iDCM with immunosuppression and/or IVIG has had mixed results.

Rationale for therapeutic apheresis

Most research on the application of apheresis in iDCM has examined IA to remove cardiac autoantibodies. CTs and CS using IA columns have demonstrated short- and long-term clinical improvement as measured by echocardiography, invasive monitoring, oxygen consumption, exercise tolerance, oxidative stress markers, B-type natriuretic peptide (BNP) levels, and standardized symptom assessments. Histologic improvements include decreased myocardial human leukocyte antigen (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 prospective case-control trial using anti-human polyclonal immunoglobulin (AHPI) IA in 17 patients found persistent reduction in β1AR 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 17 matched controls (41%, $P < .0001$; Müller, 2000). Additional economic analysis of the patients in this study found IA treatment was cost effective (Hessel, 2004). A retrospective extension of this study included 108 patients with β1AR 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 heart 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 ($P < .05$). Patients who underwent IA but who lacked β1AR antibodies had a 47% probability of being heart transplant or LVAD free at 5 years ($P < .05$; Dandel, 2012). Data from 93 patients from the Berka registry support the positive effect of IA with subsequent IVIG substitution in these patients (Ohlow, 2017). Two small RCTs with IA followed by IVIG observed improvement in heart function (Felix, 2000; Staudt, 2001). A prospective, multicenter, within-patient and parallel group, RCT of immediate versus delayed IA treatment from Japan failed to reach the primary endpoint (radionuclide LVEF improvement) but showed significant improvements for echocardiographic LVEF, NYHA score, and quality of life (Yoshikawa, 2016). A systematic review and meta-analysis of IA and/or IVIG for DCM indicates that IA treatment had a positive benefit; however, multicenter, double blinded prospective studies should be conducted to elucidate the precise effect of IA on DCM (Bian, 2021). In contrast to adults, only a few CS are available for pediatric patients (Moriguchi, 2017; Koizumi, 2017). These data seem to support that in children, as in adults, TPE treatment might be beneficial.

Based on a mixed response to treatment, investigators have searched for parameters that might predict response to IA (Bhardwaj, 2017; Ameling, 2016). Promising indicators include proteomic signatures and gene expression after IA, which might serve as predictors of who should be treated by IA. Patients with DCM due to inherited cytoskeletal abnormalities have not been treated with IA and would not be expected to respond.

Technical notes

Studies have typically included optimally medically managed patients with symptoms for ≥6 months. IVIG (0.5 g/kg) was given after the last treatment in most IA studies and one TPE CS.

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Four different IA columns (AHPI, Staphylococcal protein A agarose (SPAA), β1AR antibody, and tryptophan polyvinyl alcohol) have been used. Clinical improvement and reduction in antibody levels are observed whether using columns specific for β1AR antibody removal or nonspecific IA (Dandel, 2012). 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 (e.g., pediatric) being treated. The ideal apheresis system is not yet specified.

Volume treated: IA: 2.5- 5L depending upon the saturation and regeneration characteristics of the column TPE: 1 to 1.5 TPV

Frequency: IA: Various schedules: most commonly 5 treatments daily or every other day, TPE: 3 to 5 treatments—daily or every other day

Replacement fluid: IA: NA; TPE: albumin

Duration and discontinuation/number of procedures

There is variability in schedules for IA and TPE, with some studies repeating courses of treatment. An RCT comparing IA treatment with a single course of 5 consecutive days versus 4 courses of 5 consecutive days repeated every 4 weeks failed to demonstrate differences in LVEF at 3 and 6 months between the two treatment schemas (Staudt, 2006).

Keywords: dilated cardiomyopathy, idiopathic dilated cardiomyopathy, plasma exchange, immunoadsorption, plasmapheresis

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ERYTHROCYTOSIS

Incidence: polycythemia vera: 1/100,000/year

Indication	Procedure		Category	Grade
Polycythemia vera	Erythrocytapheresis		I	1B
Secondary erythrocytosis	Erythrocytapheresis		III	1C
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Polycythemia vera	0	3 (225)	9 (663)	NA
Secondary erythrocytosis	0	0	8 (494)	NA

Description

Absolute erythrocytosis is defined as a red blood cell (RBC) mass of at least 25% above the age and gender-specific mean predicted value, as these levels cannot be achieved with plasma volume contraction alone. Primary or autonomous erythrocytosis can be inherited or acquired. Inherited causes include primary familial and congenital polycythemia (*EPOR* mutation), Chuvash polycythemia (*VHL* mutation), congenital methemoglobinemia, high oxygen affinity hemoglobin, 2,3-bisphosphoglycerate deficiency (*BPGM* mutation), and other mutations. Acquired causes include myeloproliferative neoplasms with the *JAK2*, *MPL*, or *CALR* mutations, the common of which is polycythemia vera (PV). In PV, an abnormal hematopoietic stem cell clone autonomously overproduces RBCs. PV features include splenomegaly, granulocytosis, and thrombocytosis. Over 90% of PV cases have mutations of the *JAK2* gene, including the JAK2V16F and the JAK2 exon 12 mutations. Mutations also occur in the tumor suppressor gene, *TET2* (up to 22%). Secondary erythrocytosis occurs as a physiologic response to tissue hypoxia or inappropriate erythropoietin (EPO) secretion, which drives isolated RBC overproduction and an elevated RBC mass. Secondary erythrocytosis can occur due to a congenital erythropoietic or hemoglobin defect, chronic hypoxia related to a respiratory or cardiac disorder or residence at high altitude, ectopic endogenous erythropoietin production from a neoplasm, therapeutic erythropoietin administration, or can be idiopathic.

As the HCT level exceeds 50%, whole blood viscosity increases significantly. Symptoms of hyperviscosity include headache, 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. Increased thrombotic risk, which is encountered in 15% to 40% of patients with PV, may occur due to altered antifibrinolytic activity, clot resistance to fibrinolysis, endothelial dysfunction, and platelet activation. Risk factors for thrombotic complications include uncontrolled erythrocytosis (HCT >55%), age >60 years, and prior history of thrombosis. With PV, the 10-year risk of transformation to myelofibrosis or acute myeloid leukemia is 3% and 10%, respectively.

Current management/treatment

Management of low risk PV (age ≤60 and no prior thrombosis) includes low dose aspirin and phlebotomy, with a goal HCT ≤45%. Phlebotomy induces iron deficiency, which decreases RBC overproduction. PV is associated with extreme thrombocytosis (platelet count $>1000 \times 10^9$/L), which may precipitate increased bleeding risk due to acquired von Willebrand syndrome. Patients with high risk PV (age >60 and prior thrombosis) are treated with phlebotomy, aspirin, and cytoreductive therapy. The most often used cytoreductive agent is hydroxyurea. The JAK inhibitor, ruxolitinib, is FDA-approved for use in patients with inadequate response or intolerance to hydroxyurea. Other treatments such as busulfan and IFN-α may also be considered as second-line therapy for those patients in whom hydroxyurea is ineffective or poorly tolerated. In secondary erythrocytosis, treatment of the underlying cause is preferred. Other management strategies include long-term supplemental oxygen and/or continuous positive airway pressure maneuvers for hypoxia; surgical interventions for cardiopulmonary shunts, kidney hypoxia or an EPO-producing tumor; and ACE inhibitors or angiotensin receptor blockers for post-kidney transplantation erythrocytosis. When an underlying disorder cannot be reversed, symptomatic hyperviscosity can be treated by isovolemic phlebotomy.

Rationale for therapeutic apheresis

Erythrocytapheresis, like isovolemic phlebotomy, corrects hyperviscosity by lowering the HCT, which reduces capillary shear, increases microcirculatory blood flow, and improves tissue perfusion. The target HCT appears to be the most important risk factor for undesirable outcomes. An RCT of 365 patients with PV found that patients kept at a target HCT <45% compared to HCT 45% to 50% had significantly lower rates of cardiovascular death and major thrombosis (Marchioli, 2013). Erythrocytapheresis reduces the HCT more efficiently than simple manual phlebotomy and can increase 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. If HCT >55%, erythrocytapheresis prior to surgery can be used to reduce the high risk of perioperative thrombotic complications. A study of 76 patients with PV found platelet function improvement after erythrocytapheresis, as measured by TEG, suggesting that the hemodilution achieved with the procedure may reduce thrombotic risk (Rusak, 2012). Thrombocytapheresis, as well as erythrocytapheresis, may be indicated for patients with PV with an acute thrombohemorrhagic event associated with uncontrolled thrombocytosis and erythrocytosis. Erythrocytapheresis has also been used in the management of high altitude polycythemia and chronic mountain sickness. In a study of 32 patients with chronic mountain sickness, erythrocytapheresis significantly decreased symptoms with improvement in the 6-minute walk score (Niu, 2020).

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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. One study found that using exchange volume <15mL/kg and inlet velocity <45 mL/min, especially for patients >50 years may decrease adverse events (Bai, 2012); a proposed mathematical model for choosing most appropriate therapy parameters is available (Evers, 2014). 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 procedures

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.

Keywords: Erythrocytosis, polycythemia vera, erythrocytapheresis, blood hyperviscosity, phlebotomy, myeloproliferative disorder, myeloproliferative neoplasm

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ERYTHROPOIETIC PROTOPORPHYRIA, LIVER DISEASE

Incidence: ~2 to 5/1,000,000/year				
Procedure	**Category**		**Grade**	
TPE/RBC exchange	II		2C	
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	2 (8)*	17 (18)**

*includes patients who received both TPE and RBC exchange; **6 TPE only, 10 RBC exchange only, 2 TPE in combination with RBC exchange.

Description

Erythropoietic protoporphyria (EPP) is a rare autosomal recessive disorder characterized by reduced activity of mitochondrial ferrochelatase, the final enzyme in the heme biosynthetic pathway. Most affected individuals are compound heterozygous for a common *FECH* low expression genetic variant (IVS3-48T>C) and a second loss-of-function *FECH* mutation; a few (<5%) have bi-allelic loss-of-function mutations. Ferrochelatase catalyzes insertion of ferrous iron into protoporphyrin IX to form heme. The enzyme deficiency results in the accumulation of metal-free protoporphyrin IX (PPIX) primarily in bone marrow reticulocytes, and in circulating erythrocytes, and the plasma from which it is taken up by the liver and excreted in bile and feces. An analogous phenotype results from gain-of-function mutations in the X-linked gene, *ALAS2*, the erythroid form of the first enzyme in the heme synthetic pathway; this disease is termed X-linked protoporphyria (XLP). The diagnosis of EPP and XLP is based on demonstration of an increased level of erythrocyte total protoporphyrin IX (ePPIX) and especially metal-free PPIX. Total PPIX levels show considerable inter-individual variation depending in part on the severity of the underlying *FECH* or *ALAS2* mutations. Intra-individual variation is much less but can approach 20% over time in the absence of liver disease. Plasma porphyrins correlate roughly with erythrocyte levels but are much more variable over time, potentially reflecting more rapid turnover. EPP and XLP both present with skin photosensitivity characterized by pain, and itching after exposure to light in the blue-violet spectrum (the Soret band, ~ 410nm) which are wavelengths emitted by sunlight and some indoor light sources. These symptoms often develop within minutes of light exposure and can progress to redness and swelling. PPI is lipophilic and poorly water-soluble and is removed by hepatic clearance and biliary excretion. Liver function abnormalities are common but often not evaluated as to other etiologies in the protporphyrias. Liver failure occurs in <5% of patients and is attributed to precipitation of insoluble protoporphyrin in bile canaliculi and to protoporphyrin-induced oxidative stress. This condition is termed protoporphyric hepatopathy, and because PPIX excretion becomes impaired, levels of plasma and erythrocyte protoporphyrins and cutaneous photosensitivity can increase progressively, accelerating liver damage. Liver dysfunction from alternative causes can lead to increases in circulating levels of PPIX in EPP and XLP. Patients with XLP or with EPP due to bi-allelic loss of function *FECH* mutations with life-long higher protoporphyrin levels may face a higher risk of hepatic complications.

Current management/treatment

Treatment of the photosensitivity in patients with EPP and XLP consists mainly of avoiding light exposure (including utilizing yellow filters for some medical or surgical procedures), wearing protective clothing and barrier sunscreens. Some patients report decreased photosensitivity with β-carotene which causes a mild skin discoloration. Afamelanotide a melanocyte-stimulating hormone analogue has been shown to reduce photosensitivity and increase quality of life. Since EPP and XLP are disorders of hematopoietic cells, a cure can be achieved at present only by allogeneic hematopoietic stem cell transplantation (alloHSCT). In cases of severe liver failure, orthotopic liver transplantation (OLT) ± alloHSCT may be the treatment of choice. OLT alone does not cure the disease, and protoporphyric hepatopathy recurs in the transplanted liver. Some patients have achieved cure with OLT followed by alloSCT or rarely by alloHSCT alone after the hepatopathy responded to non-transplant medical therapy (Wang, 2021). Non-transplant medical therapies can lead to remission of protoporphyric hepatopathy or serve to bridge patients to either liver or alloHSCT.

Early treatment of protoporphyric hepatopathy has the best chance of success, particularly when patients present acutely with jaundice, abdominal pain and other features of what has been termed a "protoporphyric crisis." Such patients already have severe liver damage and their levels of PPIX in plasma and erythrocytes are increased further above their baselines. Treatment is directed toward reducing liver exposure to PPIX by reducing circulating levels, particularly in plasma, promoting more rapid biliary excretion of PPIX that has already reached the liver, and protecting hepatocytes and possibly cholangiocytes from oxidative damage. Damage to cholangiocytes is an important contributor in this disease in which cholestasis is a prominent feature.

The following treatments have been applied in various combinations in patients with protoporphyric hepatopathy: (1) oral ursodeoxycholic acid to increase biliary excretion and enhance protoporphyrin solubility in bile; (2) cholestyramine to interrupt the enterohepatic circulation of PPIX by binding it in the intestine after biliary excretion and thereby preventing its absorption into the portal circulation and return to the liver; (3) oral antioxidants (i.e., vitamin E, vitamin C, and N-acetylcysteine) to reduce oxidative damage to hepatocytes; (4) erythrocyte transfusions to reduce erythropoiesis and overproduction of PPIX in the bone marrow; (5) TPE to acutely reduce plasma porphyrin levels and thereby reduce exposure of the liver to PPIX; (6) RBC exchange to reduce erythrocyte PPIX and to take up excess plasma protopophyrins. Hemin infusions have been used in the treatment of hepatic decompensation in EPP, graft dysfunction following OLT, and in children with EPP-associated liver disease. Systematic studies assessing the impact of hemin on the bone marrow are lacking. Iron treatment should be avoided as it may upregulate ALAS2 and increase synthesis of heme precursors and heme in the marrow.

Treatment of acute, decompensated protoporphyric hepatopathy by some combination of TPE, blood transfusion, RBC exchange, cholestyramine, ursodeoxycholic acid and vitamin E is reasonable and can be guided by measuring plasma and erythrocyte protoporphyrin levels. Some combination of these treatments can also be used in patients with more chronic disease. These treatments are often used to bridge patients to OLT.

Rationale for therapeutic apheresis

The goal of TPE during acute protoporphyric liver failure is to decrease the PPIX level in the plasma and to prevent further deposition in the liver; TPE may also remove bile acids with improvement in pruritus. Some speculate that RBCs may serve as a sink to absorb excess plasma protoporphyrins, providing a rationale to consider RBC exchange to reduce plasma protoporphyrin levels. TPE and RBC exchange appear useful for patients with advanced EPP hepatopathy to prevent further protoporphyrin-mediated liver injury likely as a bridge to OLT and/or HSCT. While RBC exchange lowers the red

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blood cell protoporphyrin levels, not all case reports have shown a reduction in plasma levels (which is thought to be the source that insults the liver), suggesting that allogeneic red blood cells do not uniformly effectively absorb the excess plasma protoporphyrin. The optimal schedule and combination of TPE and RBC exchange remain unknown. Total ePPIX and total plasma porphyrin levels can be used to guide therapies (Ardalan, 2019).

Technical notes

For RBC exchange, the amount of required RBCs is based on the desired post-procedure HCT (~35%) and fraction of the original red cells remaining (FCR, ~25%-30%). Avoiding exposure of the patient to excess light during the procedure is recommended as these patients often have especially marked elevations in plasma and erythrocyte porphyrins. Hemoglobin, reticulocyte count and iron status should also be monitored.

Volume treated: TPE: 1 to 1.5 TPV; RBC exchange:1 to 1.5 RBC volume

Replacement fluid: TPE: albumin, plasma

Frequency: TPE: every 1 to 3 days;
RBC exchange: 3x/week, maintenance every week

Duration and discontinuation/number of procedures

Variable and can be guided by erythrocyte and plasma porphyrin levels, and by observing decreases to levels that are associated with improvements in liver tests. These interventions may be bridging therapies for OLT and/or alloHSCT.

Keywords: erythropoietic protoporphyria, erythropoietic protoporphyria liver, X-linked protoporphyria, porphyria, liver transplantation, RBC exchange, plasma exchange

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FAMILIAL HYPERCHOLESTEROLEMIA

Prevalence: heterozygotes: 1/200 to 300; homozygotes: 1 to 6/1,000,000

Indication	**Procedure**		**Category**	**Grade**
Homozygotes	LA		I	1A
Heterozygotes	LA		II	1A
All patients	TPE		II	1B
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
LA	6 (406)	11 (671)	NA	NA
TPE	0	1 (10)	14 (62)	NA

Description

Familial hypercholesterolemia (FH) is a common genetic cause of premature atherosclerotic cardiovascular disease (ASCVD) and comprises mutations, most commonly seen in genes encoding low-density lipoprotein receptor (LDLR), apolipoprotein B (apoB), proprotein convertase subtilisin-kexin type 9 (PCSK9), or LDLR adaptor protein 1. Patients with homozygous (HoFH) or heterozygous (HetFH) or compound heterozygous (c-HetFH) represent high-risk phenotypes, or with established ASCVD, very high-risk phenotypes. If left untreated, patients with HetFH (LDL-C typically >190 mg/dL [5 mmol/L]) develop coronary heart disease (CHD) before age 55, while homozygotes (LDL-C typically >500 mg/dL [>13mmol/L]) develop CHD early in life (average mortality at ~18 years). However, once diagnosed, lipid lowering treatment (LLT) is successful in attenuating development of ASCVD, preventing cardiovascular events, and reducing mortality in all forms of FH.

Current management/treatment

Reducing lifetime cardiovascular risk associated with accumulating cholesterol burden is the fundamental rationale for multimodal LLT in FH, which comprises lifestyle counseling, dietary restrictions, escalating combination drug therapy including statins, ezetimibe, bempedoic acid, PCSK9-inhibitors (effective in patients with residual LDLR activity), and finally LA. A substantial number of patients with HoFH, due to the mutational status of LDLR, will not adequately respond to statins or PCSK9-inhibitors. Several drugs have been shown to be effective in patients with HoFH due to their LDLR independent mechanism of action. They include lomitapide (an inhibitor of microsomal triglyceride transfer protein) and evinacumab (a monoclonal antibody targeting angiopoietin-like protein 3 [ANGPLT3]). Despite their utility in combination LLT in patients with HoFH, very high annual treatment costs may limit their use in routine care. Antisense oligonucleotide RNA-drugs are under development and have demonstrated significant reductions of LDL-C in phase I-II clinical trials (Akoumianakis, 2021; Pirillo, 2021).

There is broad consensus that HoFH should be treated as early as possible, for example, not later than age 8 years. Low body weight and vascular access represent challenges to initiating LA in small children. Guidelines of targeted LLT for adult patients mention LDL-C targets: <100 mg/dL (United States)/<70 mg/dL (Europe) for high-risk, or <70 mg/dL (United States)/<55 mg/dL (Europe) for very high-risk (Grundy, 2019; Mach, 2020).

Rationale for therapeutic apheresis

Extracorporeal elimination of lipoproteins started in 1975 using TPE, followed by the development of selective LA systems to avoid loss of beneficial plasma components and substitution of plasma products with regular treatment. Short-term effects of LA include improvement of myocardial and peripheral blood flow and endothelial function. Regular extracorporeal LDL-C elimination reduces mortality in HoFH. A CT in patients with HetFH demonstrated significant reductions in coronary events (Mabuchi, 1998). Long-term studies have demonstrated stabilization or regression of coronary atherosclerosis. LA also alters atherogenic LDL subclass distribution and decreases inflammatory mediators. These results coupled with randomized studies of LDL-C lowering drugs support that lowering LDL-C levels with LA remains essential in the prevention of atherosclerosis and cardiovascular events in patients with FH. LA can be safely initiated and/or continued during pregnancy. The use of PCSK9-inhibition for stepwise escalation of targeted LLT in FH in the context of LA treatment was investigated in two RCTs (ODYSSEY ESCAPE with alirocumab: Moriarty, 2016; DE LAVAL with evolocumab: Baum, 2019). LA was discontinued in 63% of patients, and the rate was at least halved in 93% of patients in ODYSSEY ESCAPE. In DE LAVAL, evolocumab treatment reduced LA requirement by 77% in patients with pre-LA LDL-C ≤190 mg/dL; >50% of patients achieved LDL-C <70 mg/dL. In another retrospective analysis, 44% of 25 patients treated with LA terminated regular LA after initiation of alirocumab treatment (Goldberg, 2020). However, in a real-world setting prospectively investigating 110 patients receiving PCSK9-antibodies, only 18% terminated chronic LA treatment when LDL-C target attainment was considered a major treatment goal (Spitthöver, 2019); the proportion of patients attaining the LDL-C target concentration <70 mg/dL increased by 42%. Finally, 56% of patients received a combination of PCSK9 antibody therapy and LA at individually optimized treatment frequencies. The termination of long-term LA therapy, which has hitherto prevented the progression of ASCVD, requires careful individual risk assessment and cannot be recommended by general criteria of fixed LDL-C reduction alone.

Cost-benefit considerations have a strong impact on how rigorous targeted LLT is implemented. Substantial heterogeneity exists between countries regarding eligibility criteria for LA with reimbursement regulations using different LDL-C thresholds or additionally taking severity and progression of ASCVD into consideration, for example, the FDA lists >500 mg/dL for HoFH, >300 mg/dL for HetFH, >100 mg/dL for HetFH with established CHD or peripheral artery disease (PAD), and >100 mg/dL for HetFH and lipoprotein(a) >60 mg/dL with either documented CHD or PAD (Nugent, 2020).

Despite the linear relationship between LDL-C levels and the relative risk of major coronary events, the actual practice of LA varies substantially between different countries. The availability of selective LA systems and their superior efficacy in lipoprotein removal has made the use of TPE uncommon. TPE is used in settings where LA systems are not available, or in small children where the extracorporeal volume of selective LA is too large.

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Technical notes

Selective LA systems reduce LDL-C levels by >60% to 70% after a single session. For children with body weights of 10-20 kg, experiences with selective LA systems like plasma dextran sulfate adsorption (DSA) or DFPP exist (Taylan, 2020). Priming the extracorporeal circuit with blood or plasma should be considered. Angiotensin converting enzyme inhibitors are an absolute contraindication with adsorption-based LA due to increased bradykinin generation, frequently leading to profound hypotension. Monitoring of hemoglobin, ferritin, transferrin saturation is recommended along with iron supplementation for prevention of anemia with long-term LA.

Volume treated: LA: treatment volumes vary according to recommendations of device manufacturers; TPE: 1 to 1.5 TPV

Frequency: weekly or biweekly, adjusted by individual evaluation of LDL-C target attainment; FDA has recommended to obtain an inter-apheresis LDL-C level ≤120 mg/dL

Replacement fluid: LA: NA; TPE: albumin

Duration and discontinuation/number of procedures

Chronic regular treatment every 1 to 2 weeks is clinically appropriate.

Keywords: familial hypercholesterolemia, LDL-cholesterol, lipoproteins, lipoprotein apheresis, plasma exchange, double filtration plasmapheresis.

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FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Incidence: ~7/1,000,000/year

Indication	**Procedure**	**Category**	**Grade**
Recurrent in kidney transplant	TPE/IA	I	1B
All types*	LA	II	2C
Steroid resistant in native kidney	TPE	III	2C

# reported patients: >300	**Procedure**	**RCT**	**CT**	**CS**	**CR**
Recurrent in kidney transplant	TPE	0	4 (68)	>10 (>200)	NA
	IA	0	0	11 (70)	6 (6)
All types*	LA	0	1 (23)	11 (145)	NA
Steroid resistant in native kidney	TPE	0	0	5 (54)	4 (4)

*LA data includes recurrent in kidney transplant and steroid resistant in native kidney.

Description

The term focal segmental glomerulosclerosis (FSGS) describes both a "clinical" disease characterized by primary podocyte injury, that is, primary FSGS (in most cases idiopathic), and a "pathologic" lesion (seen on microscopy) that occurs secondarily in many types of chronic kidney disease. FSGS is histologically 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. The majority (80%) of FSGS cases are idiopathic. Other causes include mutations in specific podocyte genes, medication induced, and hemodynamic adaptive response. In many cases of primary FSGS, a plasma factor (or factors) of unknown origin are postulated that injure the filtration barrier and/or increase glomerular permeability. This hypothesis is supported by the observation that FSGS may recur with a risk of 20% to 50% for first transplants, reaching 80% to 100% in repeated transplants. Soluble urokinase-type plasminogen activating receptor (suPAR) had been suggested as a major candidate for the circulating factor; however, with accumulating evidence this appears unlikely. The successful use of IA techniques with various ligands demonstrates that putative circulating factors may have immunoglobulin-like binding characteristics. Despite treatment, 30% to 60% of patients progress to end stage kidney disease within 3 to 7 years. Idiopathic FSGS poses the highest risk of recurrence post-transplant. Other risk factors for recurrence include younger age, short duration of native kidney disease, history of recurrence with previous transplant, heavy proteinuria, bilateral native nephrectomy, and living donor kidney transplants. FSGS recurrence can happen within a few hours to 2 years post-transplant. If untreated, recurrent FSGS will ultimately lead to permanent graft loss within months. Those who lose grafts to recurrence have >80% chance of recurrent FSGS in subsequent kidney transplants.

Current management/treatment

Patients with primary FSGS developing nephrotic syndrome (proteinuria >3 g/day) are treated with corticosteroids as first-line therapy, followed by calcineurin inhibitors and rituximab. Therapeutic apheresis may be considered if prior therapies have failed. For secondary FSGS, the underlying cause should be treated. The main goals of recurrent FSGS treatment is to achieve complete or partial remission of proteinuria and prevent premature allograft loss. TPE or IA is first-line therapy in recurrent FSGS and can result in partial or complete remission in >50% in children and adults. High dose corticosteroids, other immunosuppressive medications, and/or angiotensin II receptor antagonists or angiotensin-converting enzyme inhibitors represent components of drug treatment. Rituximab, IVIG, and mycophenolate mofetil have also been used in conjunction with TPE. Recurrent FSGS post kidney transplant refractory to TPE and rituximab have been treated with adjunctive ofatumumab, or abatacept, or adrenocorticotropin hormone (ACTH) analogue gel (Reynolds, 2022; Hansrivijit, 2020; Alhamad, 2019).

Rationale for therapeutic apheresis

Patients with recurrent FSGS appear to have a circulating factor that increases glomerular permeability; decreasing plasma concentration coincides with proteinuria improvement. TPE is usually started once recurrence is diagnosed. The number of TPE procedures needed to control proteinuria, a surrogate marker of FSGS, is extremely variable. The overall reported remission rate is 50% to 70%. Delayed treatment initiation (>2 weeks) appears to be more common in non-responders. Results with preemptive treatment have not been consistent. In a multicenter cohort study, 61 of 75 patients with FSGS recurrence post kidney transplant were treated with TPE (with or without rituximab) with complete or partial remission seen in 35 patients (57%) and no response in 26 patients (43%) (Uffing, 2020). Studies support the need for immunosuppression and, in some cases, ongoing TPE treatment. Some patients with recurrent FSGS have been treated with partial success with a combination of TPE and IA with staphylococcal protein A columns. In a CS using IA for early FSGS recurrence in 12 children, 10 were responders (Allard, 2018). The decrease of proteinuria occurred within the first 10 sessions after initiating IA. After 3 months of IA, 2 patients maintained remission without IA and 8 became IA dependent.

The rationale for use of LA in FSGS is based on the hypothesis that altered lipid metabolism in nephrotic syndrome resulting in hypercholesterolemia creates a lipotoxic environment affecting podocyte function (Raina, 2019). Experience is limited to CS and CRs. In the United States, LA using dextran sulfate cellulose is FDA-approved for use in the treatment of adult and pediatric patients with FSGS with nephrotic syndrome when standard treatment options, including corticosteroid and/or calcineurin inhibitor treatments, are unsuccessful, not well tolerated, or in the post-transplant setting.

Technical notes

In addition to peripheral vascular access or central venous catheters, arteriovenous fistulas or grafts (placed for prior hemodialysis) may be used for vascular access.

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Volume treated: TPE, LA, or IA with single use
adsorbers: 1.0 to 1.5 PV; IA with regenerative adsorbers: 2 to 3 PV

Replacement fluid: TPE: albumin, plasma; IA/LA: NA

Frequency: Daily or every other day at initiation of treatment; subsequent frequency and duration based on patient response

Duration and discontinuation/number of procedures

One approach is to begin with 3 daily TPEs followed by at least 6 more TPEs in the subsequent 2 to 3 weeks, although other approaches have been reported. Proteinuria is the key parameter to evaluate and monitor for response to treatment. Tapering of apheresis treatment 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. Considerations for IA treatment are essentially identical.

For LA a treatment schedule of 2 times per week for 3 weeks followed by 6 weekly treatments has been suggested. In the POLARIS study, this resulted in a response rate of 54%, which was maintained in 48% after 2 years (Muso, 2015).

Keywords: plasma exchange, immunoadsorption, lipoprotein apheresis, focal segmental glomerulosclerosis, kidney/renal transplantation

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GRAFT-VERSUS-HOST DISEASE

Incidence: after allogeneic HSCT, grade II to IV aGVHD in up to 60%; cGVHD in up to 70%

Indication	**Procedure**		**Category**	**Grade**
Acute/Chronic	ECP		II	1B
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Acute	1 (81)	6 (296)	NA	NA
Chronic	2 (148)	8 (228)	NA	NA

HSCT = hematopoietic stem cell transplant; aGVHD = acute GVHD; cGVHD = chronic GVHD.

Description

Graft-versus-host disease (GVHD) remains a major cause of morbidity and mortality following hematopoietic stem cell transplant (HSCT). The incidence of GVHD is dependent on donor, graft type, recipient age, conditioning, and post-transplant prophylaxis regimen. Acute and chronic GVHD were historically defined by the time post-transplant in which they occurred; contemporary definitions rely on clinical presentation and appearance on tissue biopsy. Overlap syndrome occurs when elements of both occur simultaneously. aGVHD manifests as inflammatory tissue injury and necrosis with skin and gastrointestinal (GI) tract inflammation and denudation, cholangiohepatic liver injury and cholestatic jaundice. cGVHD typically affects skin, GI, liver, lungs, oropharynx, eyes, genital tract and/or musculoskeletal systems without aGVHD features and has distinctive or confirmatory diagnostic criteria. aGVHD results from activation of donor T cells by host antigen-presenting cells (APCs), leading to T cell and cytokine-mediated tissue injury. Chronic GVHD is due to dysregulated allo- or autoreactive T cells, B cells, APCs and natural killer (NK) cells leading to fibrosis, inflammation, sclerosis and atrophy of affected tissues. Detailed clinical assessment and severity scores exist to systematically grade GVHD subtypes.

Current management/treatment

Both adult and pediatric cases of aGVHD (grades II-IV) and cGVHD are primarily managed with high dose corticosteroids, with or without adjunctive or second-line ECP treatment or calcineurin inhibitors. Forty to fifty percent of patients with aGVHD will be steroid refractory (SR) or steroid-intolerant (SI), requiring adjunctive treatment. Similarly, SR, SI, or steroid-dependent (SD) cGVHD cases will also require second line approaches. There is no consensus regarding optimal salvage approaches for aGVHD or cGVHD. Treatment options include ECP, mTOR-inhibitors, calcineurin inhibitors, methotrexate, mycophenolate mofetil, rituximab, infliximab, imatinib, and newer FDA approved GVHD treatment agents: ibrutinib (cGVHD), belumosudil (cGVHD), and ruxolitinib (aGVHD and cGVHD).

Rationale for therapeutic apheresis

ECP utilizes ex vivo 8-methoxypsoralen and UVA treated lymphocytes, which, when returned to the patient, 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 proinflammatory to anti-inflammatory cytokine production, and generation of regulatory T cells). The exact mechanism of ECP's anti-GVHD action is unknown.

ECP partial response rates for both aGVHD and cGVHD are approximately 65% but reported outcomes vary by treatment protocols, organ involvement site, and GVHD severity. ECP responders with either aGVHD or cGVHD show a significant survival advantage when compared to non-responders. Earlier initiation of ECP in the acute phase of inflammation may improve complete response rates.

Maximal responses for cGVHD require up to 6 months of treatment. Many clinical practice guidelines and consensus statements addressing the use of ECP for GVHD have been published and, collectively, consider ECP as an established second-line therapy option for SR aGVHD and SR/SI/SD cGVHD. Importantly, ECP treatment has no systemic immunosuppressive effects, and therefore does not increase the risk of infections, organ toxicity, or disease relapse. Additionally, ECP treatment may allow for weaning of immunosuppressant medications.

ECP may effectively improve/slow cGVHD related lung function decline in HSCT associated bronchiolitis obliterans syndrome (BOS) after standard treatment failure. Some authors recommend consideration of ECP as adjunctive first-line modality for GVHD associated BOS. Further studies are needed to confirm the efficacy of ECP, assess the optimal schedule and consider it for early treatment (see Transplantation, lung).

Technical notes

Inline/closed methods (all steps are performed in one system), offline systems (leukapheresis system for mononuclear cell (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. Two treatments in one week are often designated as one cycle. A single processed TBV performed via an offline system has also been described as a safe and efficacious cycle equivalent (Cid, 2019).

Volume treated: Varies.

Replacement fluid: NA

Frequency: aGVHD: 2 to 3 treatments weekly until response obtained (minimum of 8 weeks); cGVHD: one cycle weekly or every other week for up to 3 months, then, if responding, taper to one cycle per month to clinical response

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Duration and discontinuation/number of procedures

A variety of regimens have been used, but the majority designate two procedures within one week as a complete "cycle." For aGVHD, one cycle is routinely performed weekly until disease response (typically minimum course of 8 weeks with weekly assessments). Individualized tapering or abrupt discontinuation may be utilized following treatment response. For cGVHD one cycle is typically given weekly or every other week for up to 3 months or disease stabilization and then tapered to one cycle every 2 to 4 weeks (assess at 2-3 monthly intervals). A summary of published aGVHD and cGVHD ECP regimens is available from the Nordic ECP Quality Group (Nygaard, 2020). Prolonged ECP treatment may be beneficial.

Keywords: acute graft versus host disease, bronchiolitis obliterans syndrome, chronic graft versus host disease, extracorporeal photochemotherapy, photopheresis

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HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Incidence: 1/800,000/year (adults); 1/1,000,000/year (children)

Procedure	**Category**		**Grade**	
TPE	III		2C	
# reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
	0	1 (23)	11 (105)	28 (30)

Description

Hemophagocytic lymphohistiocytosis (HLH), also referred to as hemophagocytic syndrome or macrophage activating syndrome, 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 hemophagocytic lymphohistiocytosis [FHLH]) or secondary (reactive) after viral (EBV, CMV, H1N1, H5N1, parvovirus B19, influenza, SARS-CoV-2), bacterial (tuberculosis, *Rickettsia spp., Staphylococcus spp., E.coli*), fungal/parasitic infections (histoplasmosis, malaria, toxoplasmosis, pneumocystis pneumonia), cancer (particularly lymphoid malignancies), 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 potentially death, if untreated. The diagnosis of HLH can be challenging and requires a high index of suspicion in patients presenting with unexplainable, continuous high fever, and evidence of multiple organ involvement. The diagnosis is defined by the presence of at least five of the following eight criteria from the Histiocyte Society: (1) fever, (2) splenomegaly, (3) bicytopenia, (4) hypertriglyceridemia and/or hypofibrinogenemia, (5) infiltration with lymphocytes and histiocytes, 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 diagnosis of FHLH is made by the identification of mutations in *PRF1, UNC13D, STXBP1, RAB27A, STX11, SH2D1A*, or *XIAP*. Macrophage activation syndrome (MAS) is characterized by uncontrolled activation and proliferation of T lymphocytes and macrophages and is classified among secondary forms of HLH.

Current management/treatment

The basis of treatment of HLH is supportive intensive care according to the standards for similar life-threatening diseases, the elimination of the trigger (e.g., rituximab in EBV associated HLH after hematopoietic stem cell transplantation) and the suppression of inflammatory response and cell proliferation or both with immunosuppressive and cytotoxic drugs (cyclosporine, corticoids, etoposide, IVIG, alemtuzumab, anakinra). For FHLH in pediatric patients, HSCT is a curative option after remission is achieved with immunosuppressive therapy (standardly corticosteroids, cyclosporine and etoposide). Data from retrospective studies show encouraging treatment response of secondary HLH with corticosteroids and IVIG, both alone and in combination with etoposide, cyclosporine, and alemtuzumab. Activated recombinant factor VIIa and cytokines (G-CSF) have been used in life threatening situations with uncontrolled hemorrhage and infections risk due to DIC and granulocytopenia/thrombocytopenia. Extracorporeal treatments like TPE have been used for supportive care to stabilize organ function.

Rationale for therapeutic apheresis

The rationale for use of TPE in HLH includes removal of toxic substances as a result of organ failure (particularly liver failure) and suppression of the hyperinflammatory syndrome secondary to cytokine storm. In children with HLH one CT has been performed to date. Twenty-three children with hyperferritinemia and secondary HLH/sepsis/multiorgan disfunction (MODS)/MAS were enrolled (median number of organ failures per patient was 5). The study demonstrated that use of TPE and methylprednisolone 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%; $P = .002$; Demirkol, 2012). A comprehensive review of outcomes in adult patients with HLH showed that those who received TPE 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; Ramos-Casels, 2014). CRs suggest efficacy of TPE in HLH-associated liver failure. In one CS evaluating pediatric patients with severe EBV-related HLH, 8 patients were treated with concurrent continuous renal replacement therapy (CRRT), TPE, and chemotherapy per the HLH-2004 protocol (corticosteroids, cyclophosphamide, etoposide). Investigators found a significant reduction in circulating cytokine levels and improvement in cytopenias, ferritin levels, and other laboratory indicators. Seven children achieved partial response following CRRT/TPE and complete remission after 4 weeks except one who did not complete therapy; this was maintained for the median follow-up time of 19 months (range 15-24; Huang, 2020).

Technical notes

Volume treated: 1 to 2 TPV

Frequency: Daily, based on therapeutic goals

Replacement fluid: Albumin, plasma

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Duration and discontinuation/number of procedures

Heterogeneity of patient presentations and severity complicate determination of duration and intensity of procedures. TPE use should be tailored to local intensive care practice and clinical status of the patient.

Keywords: hemophagocytic lymphohistiocytosis, hemophagocytic syndrome, familial lymphohistiocytosis, macrophage activating syndrome, plasma exchange, plasmapheresis

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HEPARIN-INDUCED THROMBOCYTOPENIA AND THROMBOSIS

Incidence: <5% of patients exposed to heparin

Indication	Procedure		Category	Grade
Pre-procedure*	TPE/IA		III	2C
Refractory or with thrombosis	TPE		III	2C
# reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
Pre-procedure*	0	0	4 (42)	18 (20)
Refractory or with thrombosis	0	1 (44)	1 (4)	9 (9)

*Cardiopulmonary bypass, extracorporeal membrane oxygenation, and pre-transplantation.

Description

Heparin-induced thrombocytopenia and thrombosis (HIT/HITT) is a major cause of morbidity and mortality in patients receiving heparin. Thrombocytopenia classically begins 5 to 10 days after heparin exposure or within 24 hours of heparin re-exposure in individuals who were recently exposed to heparin (within the preceding 100 days). Thrombosis typically affects large vessels, with venous events more common than arterial. A 5-year epidemiological study of patients with HIT in the United States observed a thrombosis rate of ∼30% and a mortality rate of ∼10% (Dhakal, 2018). Delayed onset HIT (HIT that begins or worsens after stopping heparin) is often recognized because of thrombosis and is associated with a higher frequency of overt disseminated intravascular coagulopathy (DIC) and risk of microvascular thrombosis. In spontaneous HIT, the clinical and serological picture is consistent with HIT, but without known heparin exposure within the preceding weeks. Clinical scoring tools are helpful for HIT risk assessment, with the most commonly used being the 4Ts scoring system. A hallmark of HIT is the presence of antibodies specific for platelet factor 4 (PF4) and heparin complexes, which are identified using both immunological and functional assays. Vaccine-induced immune thrombotic thrombocytopenia (VITT) also involves PF4 antibodies (see *separate fact sheet*).

Current management/treatment

The first step in HIT management is discontinuation of all heparin products, including flushes and heparin-coated devices. Due to the continued risk of thrombosis after heparin cessation, all patients with confirmed or strongly suspected HIT (moderate to high pre-test probability) should be treated with a parenteral non-heparin anticoagulant, such as argatroban, bivalirudin, fondaparinux, or danaparoid. In the United States, danaparoid is unavailable and the only FDA-approved agents are the direct thrombin inhibitors (DTI), argatroban and bivalirudin. Though not FDA-approved for the treatment of HIT, the direct oral anticoagulants (DOACs), apixaban, rivaroxaban, and dabigatran have been increasingly investigated in limited CS and CRs.

TPE use in HIT has several indications in the literature. A cross-sectional analysis of 90 cases of TPE treatment in HIT did not identify treatment indications (Soares Ferreira Júnior, 2021); however, an international practice patterns survey (Onwuemene, 2019) and systematic review (Onuoha, 2020) identified three major TPE indications as follows: (1) primary treatment of severe HIT; (2) refractory HIT (defined as new or progressive thrombosis or persistent thrombocytopenia despite optimal management with non-heparin anticoagulants); and (3) persistent platelet-activating HIT antibodies in patients who need emergent/urgent cardiothoracic surgery on cardiopulmonary bypass (CPB) or extracorporeal membrane oxygenation (ECMO) with unfractionated heparin (UFH). UFH is preferred for CPB and ECMO due to its long record of use, short half-life, and immediate reversibility; however, UFH is contraindicated in acute or sub-acute HIT. In the setting of acute or subacute HIT where surgery cannot be delayed, consensus guidelines recommend intraoperative anticoagulation with bivalirudin; intraoperative heparin after treatment with pre-operative and/or intraoperative TPE; or intraoperative heparin in combination with a potent antiplatelet agent (Cuker, 2018).

Rationale for therapeutic apheresis

In the setting of CPB with detectable HIT antibodies indicating acute or subacute HIT, pre-CPB TPE facilitates UFH during CPB by decreasing anti-heparin/PF4 antibody complexes. The largest retrospective CS on the use of TPE in the pre-CPB setting (24 patients) showed that, for 11 evaluable patients, a single TPE treatment reduced HIT antibody titers (as measured by PF4-polyvinylsulfonate immunoassay) to negative (<0.4 OD) in seven patients (35%-85% decrease pre- to post-TPE). However, within seven days of CPB, three of these patients experienced a new thromboembolic event, two of which may have been HIT-related (Moreno-Duarte, 2020). A single CR suggests that IVIG, without TPE, may also be effective when given pre-CPB (Warkentin, 2018).

TPE has also been used in the setting of life- or limb-threatening new or progressive thrombosis in patients with HIT. The largest CT of TPE for HIT observed improved survival in patients when TPE was initiated within 4 days of thrombocytopenia. However, this study was done prior to the routine use of DTIs in HIT. In this CT, TPE resulted in a negative heparin-induced platelet aggregation (HIPA) test in >75% of all patients tested by this method (Robinson, 1999). One CR has also described the use of TPE in a patient with refractory HIT prior to stem cell transplantation. IVIG has also been used as an adjunct therapy in severe cases.

Technical notes

TPE results in a rapid decrease in platelet-activating HIT antibodies, as determined by the serotonin release assay (SRA) even in the presence of strongly reactive antibodies detected by HIT immunoassays (Warkentin, 2015). While platelet activation assays, such as the SRA, are thought to measure clinically relevant antibodies and thus, may be more helpful in guiding TPE treatment in patients with HIT, these assays may be insensitive for

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detection of some platelet-activating antibodies. While both albumin and plasma have been used for TPE, in vitro data suggests IgG containing plasma may be more effective than albumin in inhibiting HIT antibody-mediated platelet activation (Jones, 2018). Plasma may also be preferable when TPE is done immediately prior to a major procedure such as CPB surgery.

Volume treated: 1 to 1.5 TPV **Frequency:** Daily or every other day

Replacement fluid: Albumin, plasma

Duration and discontinuation/number of procedures

In the setting of CPB or refractory HIT, the number of TPE procedures performed has been heterogeneous (1-11). Some centers do several procedures that are guided by laboratory parameters or clinical response (e.g., until HIT antibody titers are reduced or become negative by the testing method used; or until resolution of thrombosis-related tissue ischemia or thrombocytopenia). However, some centers do only one TPE procedure pre-operatively or intraoperatively immediately prior to CPB.

Keywords: heparin induced thrombocytopenia and thrombosis, heparin induced thrombocytopenia, cardiopulmonary bypass, serotonin release assay, direct thrombin inhibitors, plasma exchange, thrombosis

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HEREDITARY HEMOCHROMATOSIS

Prevalence: 1/200 to 400 among people of Northern European ancestry

Procedure	Category		Grade	
Erythrocytapheresis	I		1B	
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	3 (146)	3 (223)	NA	NA

Description

Hereditary hemochromatosis (HH) includes several inherited disorders that result in iron deposition in the liver, heart, pancreas, and other organs. Genetic mutations in the *HFE* gene on chromosome 6p21 account for >95% of cases. 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. The majority of patients with HH have homozygosity for a single missense *HFE* mutation that results in substitution of cysteine with tyrosine at amino acid 282 (C282Y, type1A). Individuals with compound heterozygosity for C282Y and a histidine-to-aspartic acid substitution at amino acid position 63 (C282Y/H63D, type 1B) account for the remainder. Those who are H63D homozygous or heterozygous for the C282Y or H63D mutation alone typically do not have iron overload in the absence of other inherited or acquired conditions. Less common genetic causes of HH include mutations in hemojuvelin (*HFE2*, type 2A), hepcidin (*HAMP*, type 2B), transferrin receptor 2 (*TFR2*, type 3) and ferroportin (*SLC40A1*, type 4). Iron accumulation in HH clinically results in malaise, fatigue, arthralgia, and skin pigmentation, eventually progressing to end stage complications including diabetes mellitus, cardiomyopathy, liver fibrosis, cirrhosis, hepatocellular carcinoma, and hypogonadism. The clinical penetrance of disease is variable, with only 75% of C282Y homozygotes developing clinical symptoms and <10% with end organ damage. Diagnostic tests that are suggestive of HH include a persistent serum transferrin saturation of ≥45% and/or unexplained serum ferritin of ≥300 ng/mL in men or ≥200 ng/mL in premenopausal women. Other chronic liver diseases that can also present with iron overload include alcoholic liver disease, nonalcoholic fatty liver disease, and hepatitis C virus.

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 (≥300 ng/mL in men or ≥200 ng/mL in premenopausal women), even in the absence of symptoms or signs of end-organ damage. Typically, 500 mL of whole blood is removed weekly or biweekly until the serum ferritin is <50 ng/mL. Patients with tissue complications of hemochromatosis usually have a ferritin >1000 ng/mL and present with upward of 20 gm of excess iron. Thus, with 250 mg of iron removed per phlebotomy, two years may be needed to achieve therapeutic iron depletion. Thereafter 2 to 4 phlebotomies per year are usually adequate to maintain the ferritin ≤50 ng/mL. Malaise, fatigue, liver fibrosis, cardiomyopathy and skin pigmentation often improve with phlebotomy but treatment does not typically reverse diabetes, established joint disease or hypogonadism. 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

An RCT compared biweekly erythrocytapheresis of 350 to 800 mL of RBCs to a minimum post-procedure HCT of ≥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 ($P<.001$ and $P<.002$), 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 (Rombout-Sestrienkova, 2012). A second RCT enrolled 30 patients for biweekly erythrocytapheresis (400 mL) and 32 patients for weekly whole blood phlebotomy (450 mL). Time to normalization of ferritin to ≤50 ng/mL was equivalent; cost for erythrocytapheresis was 3x higher in this study (Sundic, 2014). A CT using another apheresis platform removed 300 to 550 mL of RBCs in patients with HCT >37%, weight >50 kg and age 18 to 65 years with mean reduction of 405 mg of iron per procedure (Grabmer, 2015). A crossover clinical trial randomized 46 patients with HH to either erythrocytapheresis or phlebotomy to keep ferritin at 50 ng/mL or below for one year and then switched groups (Rombout-Sestrienkova, 2016). In this study, mean number of procedures per treatment year was significantly higher using phlebotomy versus erythrocytapheresis (3.3 vs. 1.9; mean difference, 1.4; 95% confidence interval, 1.1-1.7). The median inter-treatment time was 2.3 times longer for erythrocytapheresis. Eighty percent of the patients expressed preference for the erythrocytapheresis over phlebotomy. The cost and ability to rapidly lower ferritin and iron stores differ by the ability of RBC reduction per apheresis procedure, which varies by apheresis technology, and patient's weight and height. The reduction in the number of required procedures per year to maintain a goal ferritin level may give a cost benefit of erythrocytapheresis over phlebotomy. In a study performed to develop a predictive model for the number of treatments needed to reach a target ferritin level, patients receiving erythrocytapheresis had 50% fewer procedures (Rombout-Sestrienkova, 2021).

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:

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

Volume treated: Erythrocytapheresis of 350 to 800 mL of RBCs

Replacement fluid: Replace at least 30% of removed RBC volume with saline if removing >500 mL

Frequency: Every 2 to 3 weeks, keeping the post-procedure hemoglobin >11 g/dL

Duration and discontinuation/number of procedures

Erythrocytapheresis every 2 to 3 weeks, or as tolerated, until serum ferritin ≤50 ng/mL. Maintenance treatment can follow with less frequent therapeutic phlebotomy or erythrocytapheresis to maintain serum ferritin levels 50 to 100 ng/mL.

Keywords: hemochromatosis, erythrocytapheresis, phlebotomy

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HYPERLEUKOCYTOSIS

Incidence: AML: WBC >100 × 10^9/L; 5% to 13% adults; ALL: WBC >400 × 10^9/L; 10% to 30% adults

Indication	Procedure		Category	Grade
	Leukocytapheresis		III	2B
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
AML	0	20 (3602)	NA	NA
ALL	0	9 (710)	NA	NA

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

Description

Hyperleukocytosis is typically defined as a circulating white blood cell (WBC) >100 × 10^9/L. In AML, hyperleukocytosis is more common with myelomonocytic or monocytic leukemia or the microgranular variant of acute promyelocytic leukemia (APL). In ALL, it associates with T cell phenotype, infants, and patient age 10-20 years. Patients with hyperleukocytosis may also present with tumor lysis syndrome (TLS), disseminated intravascular coagulopathy (DIC), and leukostasis, which is characterized by clinical evidence of decreased tissue perfusion. If unrecognized, the 1-week mortality can be as high as 40%. The diagnosis of leukostasis may be predicted clinically using a grading system (Novotny, 2005). Central nervous system manifestations include confusion, somnolence, dizziness, headache, coma, and parenchymal hemorrhage. Pulmonary complications include hypoxemia, diffuse alveolar hemorrhage, and respiratory failure. Priapism may also occur. The pathogenesis is unclear, but may relate to cell rigidity, size, rheological properties, high metabolic activity causing local hypoxia, cyto-adhesive interactions, and endothelial damage. Compared to lymphoid blasts, myeloid blasts are larger, less deformable, and have cytokine products more prone to activate inflammation and endothelial cell adhesion molecule expression. Thus, in patients with AML, leukostasis can occur when WBC >100 × 10^9/L while in ALL, it is less common and may not occur until WBC >400 × 10^9/L (Giammarco, 2017). Importantly, patients with myelomonocytic and monocytic subtypes of AML may present with symptoms when WBC >50 × 10^9/L. Leukostasis complications with other leukemias are rare but may occur with chronic myelomonocytic leukemia when the WBC >100 × 10^9/L with high LDH.

Current management/treatment

Definitive treatment of hyperleukocytosis involves the initiation of a non-specific cytoreductive agent such as hydroxyurea while awaiting final diagnosis, followed by definitive induction chemotherapy with aggressive supportive care, including TLS prophylaxis; pursuance of leukocytapheresis should not delay initiation of cytoreductive agents. Although hyperleukocytosis in AML is associated with a two- to threefold higher early mortality rate, the relative benefits of rapid cytoreduction by leukocytapheresis versus aggressive chemotherapy and supportive care alone remains poorly defined. CML during pregnancy can be treated with interferon-γ safely during the second and third trimester. The threshold to perform leukocytapheresis in asymptomatic pregnant patients with CML is unclear; a more liberal threshold of WBC 100-150 × 10^9/L has been suggested (Staley, 2018). Use of leukapheresis has been reported in small numbers in patients with CLL who have hyperleukocytosis for prevention of symptoms and in symptomatic patients.

Leukocytapheresis has been performed in patients with APL with no improvement in outcome compared to patients receiving remission induction chemotherapy. One study found that leukocytapheresis in APL may contribute to early mortality (Vahdat, 1994). Central catheter placement and invasive procedures are generally avoided in patients with APL during induction chemotherapy due to high risk of hemorrhage.

Rationale for therapeutic apheresis

Conceptually, rapid reduction of the intravascular leukemic cellular burden by leukocytapheresis would improve tissue perfusion with evidence of rapid reversal of pulmonary and CNS manifestations. However, the use of leukocytapheresis in the absence of additional cytoreductive agents may provide only very temporary, if any, reduction in circulating WBC. Several retrospective studies have been recently published evaluating the use of leukocytapheresis; none demonstrate definitive benefit on survival (Rinaldi, 2021; Gelen 2022).

Multiple retrospective studies of AML with hyperleukocytosis suggest that prophylactic leukocytapheresis might reduce the rate of early death (≤3 weeks into treatment); although there is no impact on later mortality and overall or long-term survival. Other studies have reported no benefit and raised concerns that leukocytapheresis might delay start of induction chemotherapy. A meta-analysis in patients with AML and initial WBC ≥100 × 10^9/L revealed that early mortality related to hyperleukocytosis in AML was not influenced by leukocytapheresis (Oberoi, 2014). A propensity score-matched study also showed leukocytapheresis did not have any positive influence on survival or other complications, such as TLS or DIC (Choi, 2018). A retrospective analysis in which 113 of 779 adults with newly diagnosed AML and hyperleukocytosis (>50 × 10^9/L) underwent leukocytapheresis showed no difference in 30-day mortality, remission rates, or overall survival (Stahl, 2020). A meta-analysis including 13 studies and 1743 patients with AML (486 leukapheresis/1257 chemotherapy) did not demonstrate improvement in early mortality with leukapheresis (Bewersdorf, 2020). Prophylactic leukocytapheresis has been performed for patients with AML and ALL with hyperleukocytosis lacking symptoms; no obvious benefit has been defined. In a systematic review of 11 retrospective cohort studies and meta-analysis, pooled data showed no significant difference in early mortality when comparing adults with newly diagnosed AML who did or did not undergo leukocytapheresis (Rinaldi, 2022). Limitations to these studies include the retrospective, observational nature of the publications, and having moderate to high risk of confounding bias. Leukocytapheresis may have a therapeutic role in patients presenting with leukostasis; however, chemotherapy should not be postponed and is required to prevent rapid re-accumulation of circulating blasts.

Among children and adults with ALL, clinical symptoms of leukostasis develop in <10% at WBC <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 ≥400 × 10^9/L, suggesting that prophylactic leukocytapheresis might be beneficial in that setting. Infants weighing less than 10 kg with symptomatic leukostasis due to newly diagnosed ALL can be managed with manual whole blood exchange in conjunction with agents such as hydroxyurea and steroids (Runco, 2018).

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Technical notes

A single leukocytapheresis can reduce the WBC by 30% to 60%. Erythrocyte sedimenting agents (hydroxyethyl starch, HES) are not required for AML or ALL. The use of low dose HES in leukocytapheresis is not associated with increased risk of kidney failure. RBC priming may be employed for adults with severe anemia and/or low-weight children. However, RBC transfusion(s) prior to the procedure should be avoided, if possible, since it can increase viscosity and may worsen leukostasis. Platelet, cryoprecipitate and/or plasma transfusion, however, may be given if the patient has thrombocytopenia and/or coagulopathy prior to the procedure. Replacement fluid should be used to ensure at least a net fluid balance of ±15% of TBV, especially in patients who are unstable, pregnant, or pediatric. Calcium supplementation is advisable to prevent citrate toxicity.

Volume treated: 1.5 to 2 TBV **Frequency:** Daily as needed

Replacement fluid: Crystalloid, albumin, and/or plasma as needed

Duration and discontinuation/number of procedures

For patients with AML with leukostasis, discontinue when the symptoms resolve and/or WBC $<50 \times 10^9$/L. For prophylaxis of patients with AML, discontinue treatments when the WBC $<100 \times 10^9$/L (closely monitor patients with myelomonocytic and monocytic subtypes). For patients with ALL with leukostasis, discontinue when the symptoms resolve and/or WBC $<400 \times 10^9$/L. For prophylaxis of patients with ALL, discontinue treatment when WBC $<400 \times 10^9$/L.

Keywords: hyperleukocytosis, leukostasis, leukapheresis, leukocytapheresis, acute leukemia

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HYPERTRIGLYCERIDEMIC PANCREATITIS

Incidence: 18/100,000/year

Indication	Procedure		Category	Grade
Severe	TPE/LA		III	1C
Prevention of relapse	TPE/LA		III	2C
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
TPE/LA	2 (122)	15 (1306)	NA	NA

Description

After gallstones and alcohol, hypertriglyceridemia (HTG) is the third most common cause of acute pancreatitis (AP), accounting for 4% to 10% of cases. In pregnancy, relative frequency is up to 50%. HTG-AP is a complex disorder, influenced by genetic, metabolic, environmental, and patient-specific factors. Triglyceride (TG) blood concentration is regulated by synthesis and metabolism of TG-rich lipoproteins, that is, chylomicrons reflecting enteral fat intake, and very low density lipid (VLDL) synthesized in the liver. Metabolism of TG is determined by the activity of endothelial lipoprotein-lipase (LPL) and several regulating factors. HTG-AP appears to have a more severe course than AP due to other causes, with mortality up to 30%. HTG-AP is associated with severe HTG, that is, TG levels >1,000 mg/dL (>11.3 mmol/L).

Current management/treatment

Early detection and immediate supportive management are necessary to prevent development of organ failure and limit sequelae. The revised Atlanta criteria are used to establish the diagnosis of AP, which requires two of the following: (1) abdominal pain consistent with AP, (2) serum lipase or amylase activity >3X the upper limit of normal, and (3) characteristic imaging findings of AP, and to classify severity as mild, moderate, or severe based on transient or persistent organ failure, and local or systemic complications (Banks, 2013). Correlation of AP severity and TG levels was not demonstrated using the Acute Physiology and Chronic Health Evaluation (APACHE) score (Gubensek, 2014), but became evident with the revised Atlanta criteria (Wang, 2016). Treatment for HTG and HTG-AP includes dietary restriction, lipid-lowering agents (e.g., fibrates or nicotinic acid derivatives), intravenous fluids, pain management, and the potential addition of apheresis, insulin, and/or heparin. Insulin and heparin potentially increase chylomicron breakdown and TG clearance by stimulating LPL synthesis and activity.

Rationale for therapeutic apheresis

In HTG-AP, disturbance of pancreatic microcirculation by very large TG-rich lipoproteins, with resulting ischemia, and subsequent hydrolytic release of free fatty acids are toxic to the pancreatic endothelium and acinar cells. Hypothetically, elimination of large lipoproteins reduces further organ damage. A single TPE can reduce TG levels 49% to 97%. TPE can reduce inflammatory cytokines and potentially replace deficient LPL when plasma is used. Treatment goals are to reduce TG levels to mild-moderate levels (500-1000 mg/dL). The effect of TPE is transient; adequate lipid lowering treatment is essential to achieve a persistent effect.

An RCT comparing patients with TG levels >1000 mg/dL (>11.3 mmol/L) treated with TPE versus standard of care (limited oral intake, intravenous fluids, and pain management) found TPE increased the TG clearance and decreased the time to reach TG <500 mg/L and the incidence of recurrent AP and other complications (Tang, 2021). Several retrospective case control studies have been conducted; however, the comparator groups have varied based on inclusion of insulin and/or heparin in the apheresis or comparator arm, method of apheresis, and replacement fluid (plasma and/or albumin). Patients treated with apheresis often had higher *APACHE* scores and TG levels. Systematic reviews of non-RCT, observational data found TPE did not decrease mortality, was not superior to conventional therapy, and resulted in a greater economic burden (Yan, 2022; Lin, 2022a). A two-center study comparing standard therapy (without insulin or heparin) versus TPE, observed TPE was used in patients with higher APACHE II scores, Bedside Index for Severity in Acute *Pancreatitis* (BISAP) scores, and TG levels. After propensity matching (42 patients, each arm), there were no significant differences in multiple clinical outcomes between the groups (P>.05); however, the reduction in TG in 1 day and total expenses were higher in the TPE group (P<.05) (Lin, 2022b). A study comparing double filtration plasmapheresis (DFPP) to standard therapy (some receiving insulin in both groups) observed greater reduction in TG level in 24 hours, but no impact on clinical outcomes (Lu, 2020).

An RCT for patients with non-severe prognosis and TG 15 to 40 mmol/L (1329-3543 mg/dL) randomized patients to daily TPE versus insulin infusion. This study found a non-significant trend toward a greater decrease in TG with TPE, but other clinical outcomes were similar (Gubensek, 2022). A retrospective case-control study of patients with moderate and severe HTG-AP treated with TPE (membrane based) versus insulin and heparin based on ICU location, observed no difference in lowering of TG or APACHE score and other clinical outcomes, except cost and treatment-related complications were lower in the insulin/heparin group (Jin, 2019). Compared to insulin, TPE has not consistently increased the rate of TG clearance (Yu, 2020; Dichtwald, 2021; Araz, 2022).

Apheresis has been used in patients who are pregnant (Tan, 2021) and pediatric as treatment of HTG-AP or as prophylaxis for HTG-AP; and as a maintenance therapy to sustain TG levels in the mild-moderate level to prevent further episodes of pancreatitis; and to acutely lower TG levels in the absence of AP.

Technical notes

Studies have used centrifugation- and membrane-based techniques for separation. Several selective techniques, clustered in this context as LA (e.g., DFPP, dextran-sulfate adsorption, etc.) lower lipids. Some LA techniques are optimized for the elimination of small to mid-sized apoB100-positive lipoproteins, with reduced efficacy for chylomicronemia, and may not be suitable in the acute setting with high TG levels. Small

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molecules such as free fatty acids, pancreatic lipase, and inflammatory cytokines may not be effectively removed with DFPP (Gubensek, 2021). Selective LA techniques such as DFPP might be preferred for maintenance to avoid the potential need for replacement fluids. Due to its effect on LPL activity, heparin has been suggested for procedural anticoagulant; however, many reports have used ACD-A with similar TG reductions. Albumin was frequently used as the replacement fluid. Plasma contains LPL and could enhance TG removal. Treatment has usually been implemented early in the course of HTG-AP, though some authors recommend apheresis only if there is no improvement with standard therapy. There was no difference in mortality between early and late initiation of TPE (Gubensek, 2014; Lin, 2022).

Volume treated: 1 to 1.5 TPV	**Frequency:** Daily for 1 to 3 days depending upon patient course and TG level; prophylactic use has not been investigated systematically, weekly to monthly treatment reported to maintain TG at moderate levels
Replacement fluid: Albumin, plasma	

Duration and discontinuation/number of procedures

For patients with acute HTG-AP, typically 1 to 3 TPE have been used to lower TG levels, with additional treatments if necessary. For patients treated prophylactically, chronic therapy for years has been reported.

Keywords: plasma exchange, hypertriglyceridemia, pancreatitis, chylomicronemia

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HYPERVISCOSITY IN HYPERGAMMAGLOBULINEMIA

Incidence: 5/1,000,000/year

Indication	Procedure		Category	Grade
Symptomatic	TPE		I	1B
Prophylaxis for rituximab	TPE		I	1C
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Symptomatic	0	3 (46)	>10 (>200)	NA
Prophylaxis for rituximab	0	0	3 (45)	3 (3)

Description

Blood viscosity varies as a function of hematocrit, cellular aggregation, plasma proteins, and interactions between blood and the vessel wall. As blood viscosity rises, there is a nonlinear increase in shear stress in small blood vessels, particularly at low initial shear rates. These changes damage fragile venular endothelium in the eye and other mucosal surfaces leading to the clinical sequelae of hyperviscosity syndrome (HVS). HVS is typically seen in 10% to 30% of patients with Waldenström's macroglobulinemia (WM) associated with monoclonal IgM. HVS is seen less frequently in 2% to 6% with multiple myeloma (MM) associated with monoclonal IgA or IgG3. HVS due to polyclonal hypergammaglobulinemia has been reported in Sjögren's syndrome, HIV infection, rheumatoid arthritis, autoimmune lymphoproliferative syndrome, and IgG4-related disease. HVS signs and symptoms include headache, dizziness, nystagmus, hearing loss, visual impairment (retinal hemorrhage/detachment), somnolence, coma, and seizures. Other HVS manifestations include congestive heart failure (related to plasma volume expansion), respiratory compromise, coagulation abnormalities, anemia, fatigue, peripheral polyneuropathy, and anorexia. In WM, HVS can occur when the IgM protein exceeds a concentration of 4 g/dL and the relative plasma viscosity exceeds 4 centipoise (cp; relative to water: normal range, 1.4-1.8 cp). Although serum viscosity measurements do not consistently correlate with clinical symptoms, the viscosity level at which HVS appears is generally reproducible within the same patient (symptomatic threshold). Most patients are symptomatic at levels of 6 to 7 cp. In MM, HVS occurs with plasma levels of 6-7 g/dL of monoclonal IgA or 4 g/dL of monoclonal IgG3. HVS due to polyclonal hypergammaglobulinemia is typically associated with IgG concentrations in excess of 6 g/dL.

Current management/treatment

HVS is a potentially life-threatening medical emergency that requires prompt recognition and intervention. An early HVS diagnosis is crucial to prevent further progression and can usually be made from the fundoscopic exam. The current standard of care is removal of the paraprotein by TPE which should be carried out as soon as the diagnosis is made. TPE does not affect the underlying disease process, and serum IgM levels will return to baseline in 3 to 5 weeks; therefore systemic chemotherapy or immunotherapy should be initiated soon after TPE. 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. A combination of bendamustine and rituximab has been recommended as first line therapy for bulky disease, while dexamethasone-rituximab-cyclophosphamide has been suggested as an alternative, especially in the setting of non-bulky disease. Other regimens include proteasome inhibitors (bortezomib and carfilzomib), nucleoside analogs (fludarabine and cladribine), and ibrutinib. Patients who are pregnant and unable to receive systemic therapy may be candidates for TPE.

Rationale for therapeutic apheresis

TPE has been successfully used since the late 1950s and has been shown to promptly reverse retinopathy and other HVS clinical manifestations. 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% to 30% per treatment.

A transient increase in IgM level after rituximab therapy (flares), has been reported in 30% to 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

Cascade filtration and membrane filtration techniques have been described and may have similar efficacy in removing M-protein. In IgG related hyperviscosity due to the extravascular protein concentration of IgG, significant fluid shifts may occur at the end, or shortly after the completion of a TPE procedure. Consideration can be given for the administration of additional crystalloid or colloid during or after in anticipation of this fluid shift.

Volume treated: 1 to 1.5 TPV

Frequency: Daily or every other day

Replacement fluid: Albumin, plasma

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Duration and discontinuation/number of procedures

Daily or every other day TPE until acute symptoms abate (generally 1-3 procedures). Clinical monitoring of viscosity as well as IgM or IgG levels are recommended during treatment to determine if subsequent TPE procedures are necessary. The reduction in IgM may be less than the theoretical reduction of an ideal solute (Miyamoto, 2018). Retinal changes in otherwise asymptomatic patients with WM respond dramatically to a single TPE with marked or complete reversal of the abnormal exam 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 to 4 weeks based on clinical symptoms or retinal changes may be employed to maintain clinical stability while initiating chemotherapy ± immunotherapy. Prophylactic TPE is performed to lower IgM to <4 g/dL prior to rituximab therapy.

Keywords: hyperviscosity syndrome, monoclonal gammopathy, Waldenström's macroglobulinemia, multiple myeloma, M-protein, plasma exchange

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IDIOPATHIC INFLAMMATORY MYOPATHIES

Prevalence: 1:100,000 (overall estimate for all subentities/phenotypes)

Indication	Procedure		Category	Grade
Anti-synthetase-syndrome	TPE		III	2B
Clinically amyopathic dermatomyositis				
Immune-mediated necrotizing myopathies				
# reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
	0 (0)	1 (61)	13 (85)	49 (56)

Description

Idiopathic inflammatory myopathy or myositis (IIM) designates a rare and heterogeneous group of acquired autoimmune diseases comprising dermatomyositis, polymyositis, inclusion body myositis, anti-synthetase syndrome (ASyS), and immune-mediated necrotizing myopathies (IMNM). Typical myositis symptoms include muscle weakness, abnormal muscle enzymes, and involvement of other organs. Complete syndromes are not always fully expressed at the time of presentation. IIM can also occur in the context of other autoimmune systemic diseases, termed overlap myositis. Refer to the 2016 JCA Special Issue for more information about dermatomyositis and polymyositis.

Autoantibodies, categorized as myositis-specific (MSA) or myositis-associated (MAA), are considered to play a major role in the pathogenesis of IIM, although it is not established for all subentities or phenotypes (Galindo-Feria, 2022). MSAs are associated with specific features of dermatomyositis, AsyS, and IMNM while MAAs can be found in other automimmune diseases such as SLE, Sjogren's syndrome, or systemic sclerosis. Clinically amyopathic dermatomyositis (CADM) is a subentity of dermatomyositis with typical skin manifestations (e.g., skin rash, skin ulcers, calcinosis, mechanic's hands), but little or no evidence of myositis. Echocardiography should be performed to detect myocardial involvement, found in approximately 15% of patients. Interstitial lung disease (ILD) is a hallmark, and is especially prevalent in East Asia. A major subset of patients with CADM are positive for the specific MDA5-autoantibody, which has been associated with a rapidly progressive ILD that responds poorly to immunosuppression, with approximately 50% mortality at 90 days. ASyS is characterized by autoantibodies to aminoacyl transfer RNA (tRNA) synthetases associated with a broad spectrum of organ involvement including myositis, possibly myocarditis, ILD, arthritis, and subcutaneous calcinosis. Isolated pulmonary, joint, or muscular symptoms occur as first manifestation. Misdiagnosis of ASyS as rheumatoid arthritis has been described. ILD is one of the most common clinical features and is the major contributor to morbidity and mortality in MDA5-autoantibody positive CADM and ASyS. Both can lead to rapidly progressive ILD with acute respiratory failure (ARF). Immune mediated necrotizing myopathy (IMNM) is another subentity of IIM with high creatine kinase levels, proximal muscle weakness, and absence of systemic disease. It can be divided into 3 main groups: patients with myositis who test positive to antibodies against signal recognition particle (SRP) or anti-hydroxy-3-methylglutaryl-CoA reductase (HMGCR; mostly associated with statin use), and those categorized as seronegative. IMNM have been reported, occurring with the use of immune checkpoint inhibitors (ICIs) as manifestation of off-target inflammatory and autoimmune responses.

Current management/treatment

Treatment of myositis-ILD is tailored according to ILD extent: mild-moderate, progressive and/or severe, and life-threatening using an induction-maintenance treatment approach. Pharmacological first-line therapy for all IIM consists of high-dose steroids, which depending upon response, should be tapered within six months. Combination with methotrexate, azathioprine, mycophenolate mofetil, or calcineurin inhibitors is often used. A small group of patients with IIM responds very well to first-line therapy. However, for a significant proportion of patients, long-term immunosuppression is needed to prevent irreversible tissue damage leading to permanent disability. Patients with subentities of IIM often need more intensive immunosuppression immediately following the diagnosis. Use of rituximab, Janus kinase inhibitors, and IVIG are options for refractory IIM with potential benefits. IVIG has long been used off-label, but a successful phase III RCT evaluating the long-term efficacy and safety of IVIG in adult patients with dermatomyositis led to approval by the FDA and EMA. IVIG can be particularly useful in children or if immunosuppressants are not tolerated or may not be applicable. There is also positive evidence for the use of IVIG in patients with IMNM from small studies. Combination therapy with high-dose steroids, calcineurin inhibitors, and/or cyclophosphamide represents first-line therapy in MDA5-autoantibody positive ILD. Initiating combined immunosuppression early in the disease course improves overall morbidity and mortality.

Rationale for therapeutic apheresis

The rationale for the use of TPE as part of a multimodal immunosuppressive or immunomodulating treatment for IIM is the rapid decrease of putatively pathogenic circulating antibodies, cytokines, and immune complexes to achieve clinical improvement. A double-blind, placebo-controlled trial in unspecified refractory myositis failed to show efficacy of TPE (Miller, 1992). However, since publication, IIM has been further subdivided with phenotypic variations in treatment responses. Therefore, a category IV recommendation for overall dermatomyositis/polymyositis, last published as a fact sheet in the 2016 JCA Special issue, was no longer regarded as appropriate for select IIM subentities. Inclusion body mysositis is a category IV indication described in the 2013 JCA Special Issue.

In MDA5-autoantibody positive ILD, several publications have described the benefit regarding morbidity and mortality of TPE as escalating therapeutic option following first line immunosuppressive therapies (Abe, 2020; Shirakashi, 2020; Tsuji, 2020). In these studies, TPE was performed 1 to 3 times per week, for 3 to 13 consecutive weeks with a mean number of 11.6 ± 4.0 TPE over 45.6 ± 21.0 days. Patients with MDA5-autoantibody positive ARF had a higher mortality than those with ASyS syndrome (84% vs. 18%) even when TPE was part of multimodal treatment (Vuillard, 2018).

In contrast, patients with ASyS and ILD respond well to steroids, and have a comparatively favorable prognosis with 90% achieving 5-year survival. However, with steroid treatment alone relapse of ILD can occur. Thus, a combination therapy of steroids plus immunosuppressants is often required to achieve favorable long-term disease control. Use of TPE demonstrated benefit in rare ASyS cases with ARF refractory to immunosuppressive medication.

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In a retrospective study, 6 patients with IMNM refractory to pharmacologic immunosuppression received 5 to 10 TPE treatments resulting in a significant reduction in creatinine kinase levels and symptomatic improvement. Responses in this cohort were best in patients with antibodies targeting SRP and HMGCR. ICIs are circulating with a half-life of 2-4 weeks, elimination of these pathogenic triggers could contribute to improvement. ICI use in patients with preexisting autoimmune diseases has particular risk for the development of flares of the underlying autoimmunity (see *separate fact sheet*). In overlap myositis the use of TPE should be in accordance with the use for the underlying disease.

Technical notes

Volume treated: 1 to 1.5 PV

Frequency: Daily or every other day

Replacement fluid: Albumin

Duration and discontinuation/number of procedures

Number and frequency is guided by the clinical course ranging from short-term series to extended outpatient tapers: 1 to 3 TPE per week for 3 to 13 consecutive weeks were used for MDA5-autoantibody positive CADM with rapidly progressive ILD; 5 to 10 TPE starting every other day were reported for refractory IMNM.

Keywords: myositis, inflammatory myopathy, dermatomyositis, polymyositis, anti-synthetase syndrome, necrotizing myopathy, plasma exchange, apheresis

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IgA NEPHROPATHY

Incidence: 4/100,000 with 5% to 10% developing RPGN

Indication	Procedure		Category	Grade
Crescentic	TPE		III	2B
Chronic progressive	TPE		III	2C
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	2 (24)	7 (64)	9 (11)

RPGN = rapidly progressive glomerulonephritis.

Description

Immunoglobulin A nephropathy (IgAN), previously known as Berger's disease, is the most common pattern of primary glomerular disease reported worldwide. It is frequently asymptomatic with a benign course (no severe kidney damage) but there are reports of slow progression to end stage kidney disease (ESKD) over 20 to 25 years in up to 50% of patients (chronic progressive) and, less commonly (<10%), the aggressive rapidly progressive crescentic form can occur (CreIgAN). The classic presentation is gross hematuria occurring shortly after an upper respiratory infection (synpharyngitic) or, when asymptomatic, discovery of microscopic hematuria with or without proteinuria. Characteristic kidney biopsy findings include mesangial cell and matrix proliferation on light microscopy with strong staining of IgA and often C3 predominantly in the glomerular mesangium on immunofluorescence. Factors associated with disease progression are hypertension, persistent proteinuria >1000 mg/day, and elevations in serum creatinine. CreIgAN 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 infection primes naïve B cells to class switch and become IgA antibody secreting cells (ASCs) through both T cell dependent (including the more recently described unconventional γδ T cell subset) and T cell independent (toll-like receptor [TLR] ligation) pathways, (2) some IgA ASCs mis-home to systemic compartment during lymphocyte tracking where they secrete poorly galactosylated and polymeric IgA1 into the systemic circulation, (3) this IgA1 secretion is then augmented by TLR ligation from mucosal-derived pathogen-associated molecular patterns in the systemic compartment, (4) poorly galactosylated polymeric IgA1 molecules combine with IgG and IgA autoantibodies to form immune complexes (5) the IgA1 immune complexes deposit in the mesangium which triggers a series of downstream pathways including complement activation and additional pathways that lead to glomerular injury and tubulointerstitial scarring (Floege, 2019). Glomerular IgA deposition is also seen as a secondary IgAN in a number of diseases, including alcoholic cirrhosis, celiac disease, HIV infection, and monoclonal gammopathy of renal significance as well as in conjunction with other primary glomerulonephritides. IgA vasculitis (see *separate fact sheet*; previously referred to as Henoch-Schonlein purpura) has kidney findings that are histologically identical to IgAN, however patients with IgA vasculitis typically have other extrarenal manifestations, such as rash, arthralgias, and abdominal pain.

Current management/treatment

The primary focus of IgAN management consists of use of renin-angiotensin system blockers at the maximum dose tolerated for both blood pressure control and reduction of proteinuria, omega three fatty acids, and cardiovascular risk minimization including treatment of hyperlipidemia, smoking cessation, weight control, and exercise as appropriate. Proteinuria above 0.75 to 1 g/dL despite 3 to 6 months of optimized supportive care, indicates a high risk for progressive loss of kidney function and, a 6 month course of glucocorticoid therapy could be considered. However, the clinical benefit of glucocorticoids remains controversial, and should be given with extreme caution or avoided in the setting of an eGFR <30 ml/min, diabetes, obesity, latent infections, certain secondary disease such as cirrhosis, active peptic ulcer disease, severe osteoporosis, or in uncontrolled psychiatric disease where the risks may outweigh the benefits (Rovin, 2021). Reduction of proteinuria to under 1 g/d is a surrogate marker of improved kidney outcome in IgAN. Beyond glucocorticoids, other immunosuppressive therapies are not recommended, including azathioprine, cyclophosphamide (with exception of CreIgAN), calcineurin inhibitors, and rituximab. A number of new drugs are being evaluated for IgAN, including sodium-glucose cotransporter-2 (SGLT2) inhibitors, sparsentan, atacicept, atrasentan, hydroxychloroquine, entertic coated budesonide, various complement inhibitors (e.g., eculizumab) and therapies that target B cell development. Patients with CreIgAN who have a rapid loss of kidney function should be offered cyclophosphamide and glucocorticoids; it is in this population that TPE can also be considered.

Rationale for therapeutic apheresis

The rationale for TPE in IgA nephropathy is for the removal of circulating plasma IgA-IgG complexes and complement products (C3a, C5, and soluble C5b-9). Early positive experiences of the use of TPE in treating some forms of RPGN resulted in the application of TPE to cases presenting with crescentic form. In addition, early studies demonstrated that TPE could reduce the circulating IgA and IgA immune complexes levels. Most published experience has looked solely at the treatment of the CreIgAN form of the disease and not the chronic progressive disease.

CRs and CS from previous decades have addressed the treatment of the rapidly progressive form. Most of these patients were treated with TPE and concurrent corticosteroids and/or immunosuppressants with reported improvement in kidney function and decrease in serum IgA. Several reports 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 CT examined 3 patients treated with corticosteroids and immunosuppressants and 6 who also received TPE. Two of the 3 patients who received

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only corticosteroids and immunosuppressants became dialysis dependent while the 6 receiving TPE demonstrated resolution of kidney failure during therapy. However, after discontinuation of TPE, disease progressed in all 6, with 3 being dialysis dependent at 3 years following TPE and the remaining having mild to moderate chronic kidney disease (Roccatello, 2000). This trial is representative of the experiences reported in CS and CRs.

One controlled study including 12 patients compared with 12 historical controls indicated that adding TPE to immunosuppressive therapy (glucocorticoids and cyclophosphamide) could increase kidney recovery rates in severe CreIgAN and could significantly reduce plasma IgA-IgG complex levels including complement product levels (Xie, 2016). The question of whether TPE can avoid ESKD is still open. There is one CR of a pediatric patient with rapidly progressive CreIgAN who was successfully treated with 28 sessions of IA over 2 to 3 months using antihuman Ig antibody column in conjunction with glucocorticoids, eculizumab and cyclophosphamide (Cambier, 2022). It was noted that during IA, proteinuria and IgG-IgA immune complexes decreased rapidly. Further studies are needed to define the role of IA in the management of IgAN however.

Technical notes

Volume treated: 1 to 1.5 TPV

Frequency: 6 to 9 over 21 days followed by 3 to 6 over 6 weeks

Replacement fluid: Albumin or plasma

Duration and discontinuation/number of procedures

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

Keywords: plasma exchange, plasmapheresis, IgA nephropathy, immune complex rapidly progressive glomerulonephritis, rapidly progressive glomerulonephritis

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IMMUNE CHECKPOINT INHIBITORS, IMMUNE-RELATED ADVERSE EVENTS

Incidence: 39% to 70% of patients treated with immune checkpoint inhibitors

Indication	Procedure		Category	Grade
	TPE		III*	2C
# Reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
	0	0	9 (46)	75 (75)

*Immune related adverse events due to immune checkpoint inhibitor toxicity include myasthenia gravis, thrombotic thrombocytopenic purpura (see *separate fact sheets*), myocarditis, myositis, and transverse myelitis, among other conditions.

Description

Immune checkpoint inhibitors (ICIs) are oncologic drugs that target immune checkpoint proteins and can result in immune-related adverse events (irAEs). Targeted checkpoint proteins include: (1) cytotoxic T-lymphocyte-associated protein 4 (CLTA-4), a negative regulator of T-cell activation present on CD4+ and CD8+ T cells; (2) programmed cell death-1 (PD-1), an inhibitory protein expressed on T cells, B cells, and natural killer (NK) cells, which binds to (3) programmed cell death ligand 1 (PD-L1), expressed on the surface of many tissues, including cancer cells; and (4) lymphocyte activation gene 3 (LAG3), which is expressed by B cells, some T cells, NK cells, and tumor-infiltrating lymphocytes. The mechanism of action of ICIs is to remove inhibitory signals of T cell activation so that tumor-reactive T cells overcome regulatory mechanisms to mount an effective antitumor response. FDA-approved ICIs include the anti-CTLA-4 antibody, ipilimumab; the anti-PD-1 antibodies, nivolumab, pembrolizumab, cemiplimab, and dostarlimab; the anti-PD-L1 antibodies, avelumab, durvalumab, and atezoluzumab; and the anti-LAG3 antibody, relatimab. These agents are used to treat a wide array of cancers, including breast, bladder, cervix, colon cancer, head and neck, Hodgkin lymphoma, liver cancer, lung cancer, melanoma, and Merkel cell carcinoma.

IrAEs typically occur within the first few weeks or months of ICI treatment initiation. However, ICI-induced irAEs can occur at any time during ICI therapy, including months after cessation. The pathophysiology of ICI-induced irAEs is not known but may be related to the underlying mechanism of action of the particular ICI. For example, ipilimumab, the anti-CTLA-4 agent, is more likely to cause colitis, while anti-PD-1 agents like nivolumab are more likely to cause pneumonitis and thyroiditis. It may be that ICIs interfere with mechanisms of self-tolerance and/or enhance the effects of pre-existing autoantibodies.

ICI-induced irAEs affect multiple organ systems including immune (cytokine release syndrome), neurologic (myasthenia gravis [MG]), endocrine (diabetes, thyroiditis), hepatic (acute liver failure), pulmonary (pneumonitis), cardiovascular (myocarditis), musculoskeletal (myositis), and hematologic systems (thrombotic thrombocytopenic purpura (TTP) or other thrombotic microangiopathy). A large database analysis of 7295 patients on ICI therapy revealed that ICI-induced irAE occur in 62% of patients, the most common of which were endocrine (16.4%), cardiovascular (15.7%), and pulmonary (2.5%; Brown, 2021). Although irAEs are common, they rarely cause severe toxicities leading to death. A study of the World Health Organization pharmacovigilance database, which included a systematic review and meta-analysis of the literature, found that irAE fatalities occurred in 0.3% to 1.3% of treated patients (Wang, 2018).

Current management/treatment

Based on recommendations from the American Society of Clinical Oncology (ASCO) clinical practice guidelines, treatment of ICI-induced irAE involves cessation of the ICI and initiation of corticosteroids. Duration of ICI cessation and corticosteroid dosing depend on the extent of the irAE, whether mild (grade 1), moderate (grade 2), severe (grade 3), or life-threatening (grade 4). For grade 1 irAEs, patients can be closely observed while remaining on ICI therapy. For grade 2 irAEs, ICI therapy should be stopped and, if symptoms persist after a week, corticosteroids initiated at the prednisone equivalent dose of 0.5 mg/kg daily. For grade 3 or 4 toxicities, ICI therapy should be discontinued and high dose corticosteroids initiated (prednisone equivalent of 1 to 2 mg/kg daily). If irAE symptoms fall to grade 1 or less, corticosteroids may be tapered over a 4-week period. Also, in patients who previously experienced a grade 2 or 3 irAE, ICI therapy could be restarted.

For patients who do not respond to glucocorticoid therapy within a week of ICI cessation, additional measures are warranted, including the initiation of alternative immunosuppressants such as tacrolimus, mycophenolate mofetil, and infliximab. Other immunomodulatory therapies have been used, including IVIG and TPE. In a systematic review of patients with ICI-induced MG combined with 14 patients from a single center ($n = 65$), improvement of MG symptoms was more commonly observed in patients who received intravenous IVIG or TPE as first-line therapy compared to those who received steroids alone, 95% versus 63%, $P = .011$ (Safa, 2019).

In general, depending on the organ systems involved, a multidisciplinary treatment approach is recommended. Although the above general principles apply, management of specific ICI-induced irAEs by affected organ systems are outlined in ASCO clinical practice guidelines (Brahmer, 2018; Schneider, 2021).

Rationale for therapeutic apheresis

The ICIs are monoclonal IgG antibodies with half-lives ranging from 6 days (avelumab) to 27 days (atezolizumab). These antibodies can be directly removed by TPE to decrease systemic effects. TPE is also known to remove autoantibodies that are precipitated by ICIs, including autoantibodies implicated in irAEs such as in MG, transverse myelitis, and TTP. Furthermore, TPE may further act by removing circulating

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systemic inflammatory cytokines due to ICI-induced cytokine release syndrome. A potential role for TPE may be found in its removal of circulating soluble PD-L1 and PD-L1-positive extracellular vesicles, with associated bound ICIs. In a study of patients undergoing TPE for non-oncologic reasons, TPE using albumin replacement reduced total PD-L1-positive extracellular vesicle levels by an average of 33.5%, $P<.0001$ (Orme, 2020). TPE decreased the levels by an average of 73% when the starting PD-L1-positive extracellular vesicle levels were high (>1 million). These trends were less pronounced with plasma replacement. In this study, TPE was also effective in decreasing high extracellular vesicle and soluble PD-L1 levels in patients with malignancy, including one patient on pembrolizumab and another on atezolizumab.

Technical notes

Typically, the replacement fluid is albumin. However, in patients with TTP related to ICI exposure, or in those with bleeding symptoms, plasma is recommended.

Volume treated: 1.0-1.5 TPV **Frequency:** Daily or every other day

Replacement fluid: Albumin, plasma

Duration and discontinuation/number of procedures

Duration depends on the underlying irAE. For most irAEs such as MG, myocarditis, or myositis, a minimum of 5 to 7 treatments may be needed to deplete IgG-specific antibodies.

Keywords: immune checkpoint inhibitors, therapeutic plasma exchange, plasmapheresis, and immunoadsorption

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IMMUNE THROMBOCYTOPENIA

Incidence: 20 to 40/1,000,000/year (adults); 40 to 50/1,000,000/year (children)

Indication	**Procedure**		**Category**	**Grade**
Refractory	TPE/IA		III	2C
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
TPE	0	0	6 (419)	5 (5)
IA	0	0	6 (136)	NA

Description

Immune thrombocytopenia (ITP) is the most common autoimmune hematologic disorder. ITP is an acquired thrombocytopenia in which autoantibodies or immune complexes bind to platelet surface antigens, primarily glycoprotein (GP) GPIIb/IIIa and/or GPIb/IX, to cause accelerated platelet destruction. Primary ITP, a diagnosis of exclusion, is characterized by isolated thrombocytopenia without known initiating or underlying cause. The 2019 international consensus report on ITP classified ITP as primary or secondary with further classification as follows: newly diagnosed (0 to 3 months), persistent (>3 to 12 months), and chronic ITP (lasting more than 12 months). Childhood ITP is typically acute, benign, self-limited, and presents with abrupt onset of petechiae, bruising and/or epistaxis following a viral infection. Peak age is 2 to 5 years old. For most childhood ITP, no treatment is required; however, 20% of patients will develop persistent thrombocytopenia requiring treatment. Adult ITP predominantly affects people aged 18 to 40 years, usually has an insidious onset, and results in chronic thrombocytopenia in 40% to 50%. Up to 20% of adult ITP is secondary to an underlying primary disorder or stimulus, such as systemic lupus erythematosus (SLE), lymphoproliferative disorders, drug ingestion, primary immunodeficiency or infections, especially hepatitis and human immunodeficiency virus (HIV). With the onset of the COVID-19 pandemic, the ChAdOx1 vaccine was found to be associated with small increased risks of ITP; however, causality is not established (Simpson, 2021). 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 to 60, and >60 years old, this risk is 0.4%, 1%, and 13% per patient year, respectively.

Current management/treatment

Treatment is generally not indicated when the platelet count is >20 to 30×10^9/L unless bleeding (including mucosal bleeding) occurs. First-line therapies are oral corticosteroids (1-2 mg of prednisone/kg/day), IVIG (1 g/kg/day for 1-2 days), and IV anti-RhD (50-75 μg/kg) in patients who are RhD positive. In adults, corticosteroids remain the standard primary therapy. For most children, a "watch and wait" approach is often taken after other diagnoses are excluded. For those children requiring treatment, IVIG or a single dose of anti-RhD may be substituted for prednisone to achieve a rapid response. If thrombocytopenia persists or recurs, second-line therapy includes thrombopoeitin receptor agonists, rituximab, or splenectomy. The accepted recommendation now is to treat ITP with medical management for at least one year before considering splenectomy. Fostamatinib is a spleen tyrosine kinase inhibitor recently FDA approved for the treatment of chronic ITP in patients failing at least 1 prior line of therapy. Other 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 CRs and small CS 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 (Cotter, 1983). 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 (Buskard, 1998). In a case series of 17 patients treated with corticosteroids, IVIG, and TPE, nine patients (53%) had complete response ($\geq 100 \times 10^9$ /L), seven patients (41%) had partial response ($30\text{-}100 \times 10^9$/L), and one patient (6%) had no response (Basturk, 2021). In an administrative claims database study, TPE use ($n = 372$; <1% of ITP cases) was associated with higher disease severity (OR 32.76; $P<.001$) and longer hospital stay (13 vs. 4 days; $P<.001$; Makhani 2022). IA may be considered in patients with refractory ITP, with life-threatening bleeding, or in whom splenectomy is contraindicated. IA 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 to 3 weeks with 29 (40%) 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 $50\text{-}100 \times 10^9$/L). Over half (54%) had a poor response (Snyder, 1992). The staphylococcal protein A column was removed from the market in 2006 and more recent studies with IA have used other commercially available systems. More recent studies have used TPE and IA in combination with other treatment modalities (glucocorticoids, IVIG) or as preparative treatment to achieve splenectomy in patients with severe and refractory thrombocytopenia.

In children, extra care must be given to maintain isovolemia because of the large extracorporeal volume involved in some IA systems.

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Technical notes

Volume treated: IA: 2 to 4 TPV; TPE: 1 TPV	**Frequency:** IA: Once a week or every 2 to 3 days; TPE: Daily or every other day
Replacement fluid: IA: NA; TPE: plasma or albumin	

Duration and discontinuation/number of procedures

There are no clear guidelines concerning treatment schedule and duration of treatment. The series of procedures is generally discontinued when either the patient shows improvement in platelet count $>50 \times 10^9$/L or no improvement after approximately 6 treatments.

Keywords: immune thrombocytopenia, plasma exchange, immunoadsorption

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INFLAMMATORY BOWEL DISEASE

Incidence: ulcerative colitis: 35 to 100/100,000; Crohn's disease: 27 to 48/100,000

Indication	Procedure	Category	Grade
Ulcerative colitis	Adsorptive cytapheresis	II	1B
Crohn's disease	Adsorptive cytapheresis	III	1B
	ECP	III	2C

# reported patients: >300	Procedure	RCT	CT	CS	CR
Ulcerative colitis	Adsorptive cytapheresis	14 (982)	12 (300)	NA	NA
Crohn's disease	Adsorptive cytapheresis	2 (258)	1 (104)	NA	NA
	ECP	0	0	3 (69)	2 (3)

Description

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 and northern Europe; 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-inflammatory agents, corticosteroids, 5-aminosalicylic acids (5-ASAs), tumor necrosis alpha-inhibitors (e.g., infliximab), and immunosuppressive medications (e.g., thiopurines or biologicals). Additional therapeutic agents targeting adhesion molecules and interleukins are emerging. 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. Infliximab, an FDA approved monoclonal antibody to anti-tumor necrosis factor, may induce UC and CD remission, though development of anti-drug antibodies is a known limitation to its use. Newer monoclonal antibodies including vedolizumab target integrins or adhesins to prevent leukocyte trafficking into the intestinal mucosa. Surgical intervention may be necessary in some patients.

Rationale for therapeutic apheresis

Adsorptive cytapheresis is a non-pharmacologic adjunctive treatment option for the management of active and remitting IBD with the goal of removing activated leukocytes which may contribute to IBD pathogenesis without increasing susceptibility to infections. Four systemic reviews with meta-analysis have identified a benefit of column-based granulocytapheresis as an adjunctive therapy in the induction of UC clinical remission (Habermalz, 2010; Thanaraj, 2010; Yoshino, 2014; Kiss, 2021). Conversely, one RCT showed no difference in the remission rate when adsorptive cytapheresis was compared to sham treatment (Sands, 2008), though many of the patients were lost to follow-up. Additionally, a post hoc analysis 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 patient age, disease activity level, as well as 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 large RCT did not demonstrate any difference in remission rates when compared to sham treatment in patients with moderate to severe CD (Sands, 2013). ECP has demonstrated efficacy in several immunological disorders and has been proposed as a mechanism to modulate T-regulatory cell populations in CD. Two uncontrolled CS have been published suggesting that ECP can promote remission for a proportion of patients with steroid and/or immunosuppressant intolerant CD (Abreu, 2009; Reinisch, 2013). The Japanese Society for Apheresis guidelines have issued Category II, 1B and Category II, 2B recommendations for the use of adsorptive cytapheresis in the treatment of UC and CD, respectively (Ade, 2021).

Technical notes

Two types of adsorptive cytapheresis devices used primarily in Europe and Japan are the leukocytapheresis Cellsorba (Asahi Medical, Tokyo, Japan), a filtering column containing cylindrical non-woven polyester fibers and, the granulocyte/monocyteapheresis Adacolumn (JIMRO, Japan), a selective adsorption column containing cellulose-coated acetate beads. Both require anticoagulation (heparin/ACD-A and heparin alone, respectively) to remove granulocytes and monocytes from venous whole blood by filtration/adhesion. For Cellsorba, venous whole blood is processed at 50 mL/min through the column for 60 minutes. Some platelets and lymphocytes are also removed by this column. For Adacolumn, venous whole blood is processed at 30 mL/min for 60 to 90 minutes. 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 Japan. The two columns have been compared in a prospective CT and an RCT, demonstrating equivalent response in patients with moderate-to-severe active UC (Sakata, 2008; Yamasaki, 2019). CS and CRs have described ECP in the treatment of treatment-refractory CD, but no consensus regarding treatment approaches has been identified. CRs have also described the successful use of leukocytapheresis series in the treatment of severe steroid dependent UC.

Volume treated: Adacolumn: 1800 mL; Cellsorba: 3000 mL: ECP: varies

Replacement fluid: NA

Frequency: Once per week, more intensive therapy may include daily or two times/week

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Duration and discontinuation/number of procedures

The typical length of treatment is 5 to 10 weeks for Adacolumn and 5 weeks for Cellsorba. Aforementioned case series utilized ECP on the following schedules, respectively: twice weekly, every week for 4 weeks, followed by twice weekly, every other week for 7 weeks and two ECP treatments every two weeks for 24-weeks.

Keywords: Adacolumn, Cellsorba, granulocyte and monocyte adsorption apheresis, leukocytapheresis, selective apheresis, adoptive cytapheresis, granulocyte monocyte adsorptive apheresis, leukocytapheresis, Crohn's disease, ulcerative colitis, inflammatory bowel disease

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LAMBERT-EATON MYASTHENIC SYNDROME

Incidence: 2 to 4/1,000,000

Procedure	Category		Grade	
TPE	II		2C	
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	7 (43)	9 (11)

Description

Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune disorder affecting the pre-synaptic neuromuscular junction (NMJ). Its classical clinical triad includes muscle weakness (most prominent in proximal muscles of the lower extremities), hyporeflexia, and autonomic dysfunction. In contrast to myasthenia gravis (MG), brain stem symptoms such as diplopia and dysarthria are uncommon. Also, on examination, there is an increase of maximal gripping power over the initial 2 to 3 seconds (Lambert's sign). LEMS cases are classified into non-paraneoplastic or paraneoplastic (approximately 60% of the cases). Paraneoplastic cases are most commonly associated with small cell lung cancer (SCLC). Other cancers reported in association with LEMS include lymphoproliferative disorders, thymic cancers, prostate carcinoma, and Merkel cell carcinoma. Rapid onset and progression of symptoms over weeks or months should heighten suspicion of underlying malignancy. While SCLC-LEMS typically presents at a median age of 60 years, non-paraneoplastic LEMS has a bimodal distribution (first peak around 35 years and second peak around 60 years).

The diagnosis of LEMS is confirmed by electrodiagnostic studies. In 85% to 90% of patients, there are autoantibodies directed at the P/Q type voltage-gated calcium channel (VGCC) of the NMJ (Titulaer, 2011). These antibodies are believed to cause insufficient release of acetylcholine quanta by action potentials arriving at motor nerve terminals; however, the presence of antibodies alone is not diagnostic. Unlike MG, which is characterized by antibodies to the postsynaptic acetylcholine receptor, VGCC antibodies target the pre-synaptic structure. Antibody levels do not correlate with severity but may decrease as the disease improves in response to immunosuppressive therapy. SRY-Box 1 (SOX1) antibodies are an additional characteristic of 65% of patients with paraneoplastic LEMS. Similarly, N-type VGCC and $GABA_B$ receptor antibodies are associated with higher risk of paraneoplastic LEMS. The DELTA-P (Dutch-English LEMS Tumor Association Prediction) clinical score can be used to identify those at risk of SCLC.

Current management/treatment

Apart from evaluation and treatment of primary malignancy, management of LEMS is directed toward increasing acetylcholine availability at post-synaptic membrane to improve neurological function and immunosuppression to control production of the autoantibodies. Amifampridine [3,4-DAP (3,4-Diaminopyridine) or 3,4-DAP phosphate] is the first choice for symptomatic control in LEMS. These medications block fast voltage-gated potassium channels, prolonging presynaptic depolarization and thus, the action potential, resulting in increased calcium entry into presynaptic neurons and increased release of acetylcholine. Cholinesterase inhibitors such as pyridostigmine can also be used; but, when compared to their use in MG, tend to be less effective when given alone. Although beneficial, guanidine's use is limited by toxicity.

If symptomatic therapy is unsatisfactory, immunosuppression is indicated. Recommendations for immunosuppressive therapies include oral corticosteroids, azathioprine, cyclosporine, IVIG, and TPE. Studies have reported significant improvement following combination treatment with corticosteroids and azathioprine (Newsom-Davis, 1984). In a randomized, double-blind, placebo-controlled crossover trial involving 9 patients, IVIG has been shown to be an effective treatment (Bain, 1996). IVIG may be useful when given as monthly infusions of 2 g/kg (over 2-5 days) for 2 or more years. In some cases, rituximab is effective; however, it is usually reserved for patients who have failed other immunosuppressive treatments. It should be noted that, in most cases, LEMS requires long-term treatment.

Rationale for therapeutic apheresis

Once LEMS was identified as an autoantibody-mediated syndrome, there have been several attempts to use TPE in its treatment. While no CTs exist on the use of TPE in LEMS, CS have suggested a benefit. In one CS, 8 out 9 patients, the electromyographic muscle action potential increased ($P<.01$) while receiving TPE and immunosuppression (Newsom-Davis, 1984). These patients demonstrated rapid (~2 weeks) but transient improvement (~6 weeks) with TPE. Moreover, patients tended to worsen after completion of TPE if additional immunosuppressive therapy was not given. TPE may be a useful adjunct to management of patients with LEMS whose neurological deficit is severe or rapidly developing. TPE may be especially helpful in the case of patients who are unable to wait for immunosuppressive medications or amifampridine to take effect, or when IVIG is not feasible. In a long-term analysis of 150 patients, exacerbations requiring emergency treatment with TPE occurred in 27% of patients, overall once in every 16 patient-years of follow-up (Lipka, 2020). IA might be an alternative treatment option; however, data are even more limited for IA than for TPE (Sauter, 2010).

Technical notes

Volume treated: 1 to 1.5 TPV

Frequency: Daily or every other day

Replacement fluid: Albumin

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Duration and discontinuation/number of procedures:

Treatment should continue until a clear clinical and EMG response is obtained or at least until a 2 to 3-week course of TPE has been completed. Repeated courses may be applied in case of neurological relapse, with effects lasting up to 6 weeks in the absence of immunosuppressive therapy. The reported TPE regimens vary, 5 to 7 TPEs over 10 to 14 days is a reasonable course to start. Regimens are typically adjusted to symptom response. Longer course may be necessary (5-15 TPEs over 4-19 days; Newsom-Davis, 1984). Of note, after initiation of TPE, improvement may not be seen for 2 weeks or more, potentially due to the slower turnover of the presynaptic VGCC compared to the postsynaptic acetylcholine receptor.

Keywords: Lambert-Eaton myasthenic syndrome, plasma exchange, plasmapheresis, immunoadsorption

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LIPOPROTEIN(a) HYPERLIPOPROTEINEMIA

Prevalence: ~20% lipoprotein(a) levels >50 mg/dL

Indication	Procedure		Category	Grade
Progressive atherosclerotic cardiovascular disease	LA		II	1B
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	3 (61)	4 (317)	NA	NA

Description

After the first description of lipoprotein(a) [Lp(a)] in 1963, the Copenhagen City Heart-Study in 2008 was seminal for recognizing Lp(a) as an independent and causal risk factor of atherosclerotic cardiovascular disease (ASCVD) in the general population (i.e., coronary artery disease, calcific aortic valve stenosis, peripheral arterial disease, and stroke). Subsequent pathophysiological research, epidemiologic studies, and Mendelian randomization studies confirmed this role.

Lp(a) is composed of an LDL-like particle to which a single copy of apolipoprotein(a) [apo(a), encoded by the *LPA*-gene] is covalently attached. The physiological function of Lp(a) is still unknown. Apo(a) is composed of an inactive protease domain and plasminogen-like kringle IV (KIV) domains. Ten different KIV domains have evolved in the *LPA* gene, which show an extensive repeat copy number variation resulting in >40 Lp(a) isoforms of different sizes. In approximately 80%, *LPA* is heterozygous, with more abundant expression of the smaller isoform. The number of circulating Lp(a)-particles is mainly genetically determined with significant differences of Lp(a) concentration and isoform distribution among populations. Lp(a) concentration and isoform size are inversely correlated. Patients with familial hypercholesterolemia typically have higher mean Lp(a) concentrations. Kidney disease can also lead to increased Lp(a) levels.

Lp(a) exerts all atherogenic effects of an LDL-particle. Bound oxidized phospholipids, accumulation in atherosclerotic plaques, and antifibrinolytic effects are additional features. Current scientific statements by the American Heart Association and European Atherosclerosis Society conclude that elevated levels of Lp(a) are an independent and causal risk factor for ASCVD even with effective reduction of plasma LDL-C and apoB100 (Koronenberg, 2022, Reyes-Soffer, 2022). The BIOSIGNAL study showed that elevated Lp(a) was independently associated with large artery atherosclerosis stroke and risk of recurrent cerebrovascular events among individuals <60 years old or with history of ASCVD (Arnold, 2021).

Current management/treatment

Lp(a) concentration above 50 mg/dL confers clinically relevant ASCVD risk. Diet or lifestyle have no influence on Lp(a) concentration and there are currently no drugs approved to treat Lp(a)-hyperlipoproteinemia [Lp(a)-HLP]. Existing lipid lowering drugs reduce Lp(a) concentration to varying extents, however, the clinical relevance of this effect is unknown: nicotinic acid by ~39%, and PCSK9-inhibitors including alirocumab, evolocumab, or inclisiran, up to 30%. Statins or bempedoic acid have no relevant effect. The FOURIER trial showed that patients with baseline Lp(a) in the highest quartile had a higher risk of coronary heart disease (CHD) death, myocardial infarction (MI), or urgent revascularization independent of LDL-C levels; evolocumab reduced Lp(a) by a median of 26.9% and risk of the composite of CHD death, MI, and urgent revascularization by 23% in patients with baseline Lp(a) >median (O'Donoghue, 2019). The ODYSSEY OUTCOMES trial demonstrated risk of peripheral artery disease (PAD) events was related to baseline quartile of Lp(a) ($p_{trend} = 0.0021$), and both Lp(a) and PAD events were reduced by alirocumab (23.5% and 31%, respectively; Schwartz, 2020). Statistical modeling from ODYSSEY OUTCOMES hypothesizes that Lp(a) lowering by PCSK9-antibodies might represent an independent effect on ASCVD risk reduction (Bittner, 2020). Antisense oligonucleotides (ASOs) inhibiting apo(a) synthesis and Lp(a) production (such as pelacarsen, formerly AKCEA-APO(a)-L_{Rx}) have shown promising results in phase II clinical trials with up to 80% reduction (Tsimikas, 2020). Small interfering RNA (siRNA) molecules such as olpasiran, formerly AMG890, and SLN360 are in phase I and II trials (Swerdlow, 2022).

Rationale for therapeutic apheresis

All currently available LA systems can decrease Lp(a) >60% to 80% after a single session. A few RCTs and CTs have investigated the use of LA in patients with Lp(a)-HLP and demonstrated relief of refractory angina, improved myocardial perfusion, regression of coronary stenosis, or increased patency of vein grafts after coronary artery bypass graft (Safarova, 2013; Ezhov, 2017). Analysis of an RCT of 20 patients with refractory angina and Lp(a) >50 mg/dl, comparing the effect of 3 months of blinded weekly LA (vs. sham LA), found a 30% decrease in oxidized LDL ($P<.0001$) and 22% decrease in anti-oxidized LDL IgG and IgM antibodies ($P \leq .012$) in the LA treated cohort (Khan, 2021). Several studies used the design of comparing incidence rates of cardiovascular events, before and after commencing chronic LA treatment of patients with Lp(a)-HLP and severe ASCVD, with observation periods of 2 to 5 years (Moriarty, 2019). Using patients as their own controls, results consistently demonstrated that LA treatment has been highly effective in preventing cardiovascular events. In the 5-year prospective follow-up of the Pro(a)LiFe study (a major study of the efficacy of long-term LA for the prevention of ASCVD complications in patients with Lp(a)-HLP and prior progressive ASCVD), no findings of aortic valve stenosis (AVS) were reported despite evidence that Lp(a)-HLP is an independent risk factor for progressive calcific AVS (Roeseler, 2016).

Given the prevalence of elevated Lp(a) levels in the general population, additional criteria are mandatory for the indication of Lp(a) lowering treatments, including LA. The 2008 German reimbursement guideline introduced the Lp(a) threshold >60 mg/dL associated with progressive ASCVD (Leebmann, 2013). In April, 2020, the US FDA approved the use of LA for patients (on maximal tolerated combination drug therapy) with LDL-C >100 mg/dL and Lp(a) >60 mg/dL, and either documented CHD or PAD (Nugent, 2020). Positive family history, or premature manifestation of ASCVD, are important aspects when considering Lp(a) associated cardiovascular risk. Attributing Lp(a) as the major risk factor for progression of ASCVD in an individual patient requires all other cardiovascular risk factors (including LDL-C) be under optimized treatment (Grundy, 2019; Mach, 2020).

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Technical notes

Angiotensin-converting enzyme inhibitors are contraindicated in patients undergoing adsorption-based LA due to increased bradykinin generation, leading to profound hypotension.

Volume treated: Plasma or whole blood volumes vary according to recommendations of device manufacturers.

Frequency: Once every 1-2 weeks

Replacement fluid: NA

Duration and discontinuation/number of procedures

Treatment is continued indefinitely. Lp(a) target levels to guide LA frequency; time averaged or post-LA concentration have not been defined. A single session should have >60% reduction of pre-LA Lp(a) concentration.

Keywords: LDL apheresis, lipoprotein apheresis, lipoprotein(a), Lp(a), apolipoprotein(a), coronary heart disease, cardiovascular disease, hyperlipoproteinemia.

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MALARIA

Incidence: 241 million cases worldwide in 2020; ~2000 cases in United States annually

Indication	Procedure		Category	Grade
Severe	RBC exchange		III	2B
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
RBC exchange	0	1 (415)*	NA	NA
Manual exchange transfusion	0	8 (279)	9 (128)	NA

*Includes both automated and manual RBC exchange.

Description

Malaria is a mosquito-borne protozoal infection caused by *Plasmodium vivax, P. ovale, P. malariae*, or *P. falciparum*. The estimated number of deaths worldwide from malaria stood at 627,000 in 2020. The highest mortality occurs with *P. falciparum* in Africa with children <5 years accounting for 80% of malarial deaths. Most cases in the United States are in travelers and immigrants returning from countries where malaria transmission occurs, many from Sub-Saharan Africa and South Asia. 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 *P. falciparum* malaria is 5% to 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

Treatment is based on clinical status of the patient, infecting *Plasmodium sp*., drug-susceptibility pattern predicted by geographic region of acquisition, and prior use of antimalarials including, malaria chemoprophylaxis. Management of imported uncomplicated malaria in the United States is outlined in guideline documents available from the US Center for Disease Contraol and Prevention (CDC) and includes artemisinin-based combination therapy (ACT). Severe malaria should be treated promptly with intravenous artesunate which can be obtained through the CDC if commercial artesunate is not readily available. Until artesunate is acquired, interim oral treatment with artemether-lumefantrine, atovaquone-proguanil, quinine, or mefloquine should be initiated. Treatment may require instillation through a nasogastric tube in comatose patients. Intensive care support is often necessary.

Rationale for therapeutic apheresis

RBC exchange or manual exchange transfusion (ET) 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. ET may also reduce pathogenic humoral mediators, such as parasite and host toxins, hemolytic metabolites, and cytokines. RBC exchange in patients infected with malaria has been introduced more than 40 years ago, however, to date no RCT has ever been performed. 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 8 CTs found no survival benefit of manual ET compared to antimalarials and aggressive supportive care (Riddle, 2002). 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 vs. automatic, full or partial; whole blood vs. RBC), lack of parasitemia level in many patients, lack of survival data in patients treated with ET, exclusion of ET survival cases, and imperfect matching of cases and controls (Tan, 2013). Based on this study, the CDC no longer recommends exchange transfusion for the treatment of severe malaria. The 2016 United Kingdom treatment guidelines for severe malaria also no longer recommend exchange transfusion, citing the rapid action of artesunate in reducing parasite burden. The World Health Organization (WHO) guidelines in 2021 make no recommendation regarding ET use, citing lack of consensus on indications, benefits, dangers, and practical technical details. Few reports have described using adjunctive TPE with or without automated RBC exchange potential benefits being attributed to the removal of toxins or cytokines.

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% to 15% of the original. The additional risks in developing countries may include transfusion-transmitted infections.

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Volume treated: 1 to 2 total RBC volumes **Frequency:** 1 to 2 treatments

Replacement fluid: RBCs (consider leukoreduced)

Duration and discontinuation/number of procedures

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

Keywords: malaria, RBC exchange, exchange transfusion, falciparum

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MULTIPLE SCLEROSIS

Prevalence: 300/100,000 (United States)

Indication	Procedure	Category	Grade
Acute attack/relapse	TPE	II	1A
	IA	II	1B
Chronic primary or secondary progressive	TPE/IA	III	2B

# reported patients: >300	Procedure	RCT	CT	CS	CR
Acute attack/relapse	TPE	4 (237)	2 (189)	NA	NA
	IA	2 (99)	4 (273)	NA	NA
Chronic primary or secondary progressive	TPE	4 (300)	2 (50)	NA	NA
	IA	0	0	2 (27)	0

Description

Multiple sclerosis (MS) is the most prevalent chronic inflammatory demyelinating disease of the central nervous system (CNS) and is a leading cause of disability in young adults. Compared to the general population, life expectancy in patients with MS is reduced by 7 to 14 years. Typical symptoms at presentation include, but are not limited to, monocular painful visual loss (due to optic neuritis), limb weakness or sensory loss (due to transverse myelitis), double vision (due to brain-stem dysfunction), or ataxia (due to a cerebellar lesion). The presenting feature in 15% to 20% of patients is acute demyelinating optic neuritis, which occurs in 50% of patients at some time after disease onset. The clinical course can be classified as clinically isolated syndrome (CIS; the first clinical episode suggestive of MS), relapsing-remitting (RRMS; most common type at onset), and primary or secondary progressive (PPMS/SPMS). After 10 to 20 years from RRMS, many patients develop a progressive course (SPMS), which leads to neurologic disability; however, approximately 10% of patients with MS have a progressive course (PPMS) from the onset of the disease. MS lesions can appear throughout the CNS and are recognized in the white matter as focal areas of demyelination, inflammation, and glial reaction. Though not fully elucidated, MS pathophysiology is thought to be mediated by humoral and cell mediated autoimmunity as well as genetic and environmental factors (including EBV infection). MS is primarily a clinical diagnosis with the primary diagnostic test of choice being MRI. Additionally, McDonald criteria can be useful in assisting with making the clinical diagnosis (Thompson, 2018). Poor prognostic factors include primary progressive form, bowel/bladder symptoms at onset, and incomplete recovery from first attack; however, there are no factors that reliably predict the disease course.

Current management/treatment

Standard treatment for CIS or acute MS attacks or relapses is high dose glucocorticoids. When systemic glucocorticoids are contraindicated, corticotropin injection gel can be an alternative. In 20% to 25% of patients who do not respond to steroids after an interval of 10 to 14 days, treatment with therapeutic apheresis should be considered.

An increasing number of disease-modifying therapies (DMT) have become available in recent years, including preparations of interferon beta, immune modulating monoclonal antibodies, and chemotherapeutic agents. These agents reduce the likelihood of inflammation and injury, relapses, neurological impairment and disability. Based on the ability of several of these drugs to lower long-term risk of disease progression, early treatment is recommended; however, there is no consensus on method of selecting initial treatment.

Rationale for therapeutic apheresis

TPE or IA may benefit patients with MS by the immediate removal of plasma-based antibodies and immune complexes, induction of a redistribution of antibodies from the extravascular space, and subsequent immunomodulatory changes. Early active MS lesions can be classified into four immunohistopathological patterns (Lucchinetti, 2000). Pattern II lesions are selectively associated with immunoglobulins and complement deposited along myelin sheaths, which predict the best response to TPE or IA as shown in patients with steroid-unresponsive relapse and availability of biopsies (Stork, 2018). However, clinical, radiographic, or biomarkers that reliably differentiate immunopathological patterns or disease mechanisms are not currently available.

According to United States and European recommendations, TPE is indicated in acute, severe MS acute attacks or relapses with RRMS/SPMS not responsive to initial treatment with high-dose steroids (Multiple Sclerosis Therapy Consensus Group, 2008). Overall results with RRMS are better compared to SPMS (Magana, 2011, Lipphardt, 2019). Clinical improvement may not be accompanied by resolution of active lesions on imaging. Recovery of visual acuity in cases with optic neuritis was a prominent clinical result (Koziolek, 2012).

Use of IA in acute attack/relapse of MS has also been reported. In a RCT of 61 patients with steroid-refractory relapse or CIS, compared to those who received TPE, patients who received IA had similar immediate improvement after treatment weeks 1 and 2. At week 4, patients assigned to IA had more significant improvement in their Multiple Sclerosis Functional Composite score; however, patients in the TPE group received lower PV exchanged during each treatment (average 0.69 PV) versus the IA group (2-2.5 PV; Dorst, 2019). Another study showed that patients who received IA had better outcomes versus those who received double-dose methylprednisolone in steroid-refractory acute relapses (Pfeuffer, 2022). Other retrospective studies also suggest that IA has similar efficacy to TPE, while also preserving valuable plasma proteins and avoiding plasma products-associated risks (Heigl, 2013; Schimrigk, 2016). The safety profile of IA is also generally not different from TPE regarding transient hypotension or central vascular access complications.

In pregnancy, apheresis can be considered since currently available disease modifying therapies for MS are contraindicated. Furthermore, steroid pulse therapy can also have severe side effects for the embryo or the mother. In a recent retrospective analysis, 83% of patients showed a marked improvement of relapse symptoms after IA during pregnancy or breastfeeding (Hoffmann, 2018).

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In contrast to acute attacks/relapses, other therapies (such as disease-modifying therapy) should be considered for patients with chronic PPMS/SPMS as TPE is generally regarded as ineffective in these patients based upon results of several RCTs (Vamvakas, 1995); however, it may be beneficial in carefully selected group of patients (Khatri, 2014).

Technical notes

Almost all studies on IA in MS used single-use tryptophan adsorbers.

Volume treated: 1 to 1.5 TPV with TPE; 2 to 2.5 liters for tryptophan-IA (manufacturer's recommendation); up to 2.5 TPV with regenerative immune adsorbers

Frequency: Acute attack/relapse: 5 to 7 over 10 to 14 days

Replacement fluid: TPE: albumin; IA: NA

Duration and discontinuation/number of procedures

In acute MS attack/relapse unresponsive to steroids, 5 to 7 TPE or IA procedures typically have a response rate of >50%. Early treatment initiation, within 14 to 20 days of symptom onset, predicts response.

Keywords: multiple sclerosis, multiple sclerosis therapy, optic neuritis, plasma exchange, acute CNS demyelinating disease, immunoadsorption

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MYASTHENIA GRAVIS

Incidence: 7 to 23/million				
Indication	**Procedure**		**Category**	**Grade**
Acute, short-term treatment*	TPE/DFPP/IA		I	1B
Long-term treatment	TPE/DFPP/IA		II	2B
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
TPE/DFPP	11 (434)	12 (561)	NA	NA
IA	1 (19)	5 (131)	>10 (>200)	NA

*For moderate-severe disease (i.e., myasthenic crisis, unstable or refractory disease) and unstable pre-thymectomy.

Description

Myasthenia gravis (MG) is an autoimmune disease in which antibodies bind to acetylcholine receptors (AChR) or to functionally related molecules in the postsynaptic membrane at the neuromuscular junction and in skeletal muscle. The antibodies induce fluctuating weakness of skeletal muscles, which typically worsens later in the day, after repetitive muscle use, or after exercise. MG can be generalized or localized, and usually involves the eye muscles, causing diplopia and ptosis. Ten percent of patients with MG also have a thymoma. MG can be early-onset (occurring in the 2nd and 3rd decades) or late-onset (6th to 8th decades). Juvenile MG is defined by onset before age 15 years. Rare cases have been described in neonates due to passive maternal antibody transfer. Of note, MG has been reported to occur in association with COVID-19; however, the diagnosis and management are similar to other MG subgroups.

The MG diagnosis is confirmed by the combination of typical symptoms and a positive autoantibody test. Antibodies that are both specific and sensitive for MG detection and define disease subgroups include antibodies against AChR (~85%, usually associated with thymoma), muscle-specific kinase (MuSK, ~8%, usually not associated with thymoma and often more severe), and lipoprotein receptor-related protein 4 (LRP4, ~1%, less severe MG). More severe disease may be suggested by antibodies against titin, agrin, and ryanodine receptors. In antibody-negative cases (~6%), the diagnosis is confirmed by neurophysiological tests and a characteristic response to therapy. Myasthenic crisis still represents a serious, life-threatening event (mortality ~5%-10%) characterized by rapid worsening of MG and airway compromise from ventilatory or bulbar dysfunction, requiring mechanical on non-invasive ventilation.

Current management/treatment

Increasing use of immunomodulating therapies has been a major factor in improving the prognosis for patients with MG. Therapy should be aimed at full or nearly full remission. Major treatment approaches include anticholinesterase inhibitors, thymectomy, immunosuppression, and either apheresis or IVIG as rapid but short-acting immunomodulating therapy. For all MG subgroups, first line treatment is acetylcholinesterase inhibition. Dose limiting factors are cholinergic side effects, including diarrhea, abdominal cramping, increased salivation, sweating and bradycardia. Thymectomy is usually indicated in patients with thymoma or generalized AChR-positive MG adults ≤50 years and can result in clinical improvement and reduce the need for immunosuppression. Decision on thymectomy in other MG subgroups (e.g., older patients, patients without AChR antibodies) should be individualized. Immunosuppressive drugs are usually given in patients who remain symptomatic with anticholinesterase therapy and/or for long-term management. These therapies include glucocorticoids or glucocorticoid-sparing treatments, such as azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus and methotrexate. Ravulizumab and eculizumab, terminal complement inhibitors, and efgartigimod, a neonatal Fc receptor antagonist were FDA approved for the treatment of generalized MG in adults who are AChR antibody positive. The impact of these drugs as alternative to apheresis or IVIG remains to be established. MuSK-positive MG tends to be poorly responsive to anticholinesterase inhibitors and may benefit from early initiation of rituximab. Approximately 10% patients with severe MG may be refractory to first-line immunotherapies and thus, rituximab, cyclophosphamide, and maintenance IVIG or apheresis can be considered.

Rationale for therapeutic apheresis

Apheresis (TPE, DFPP or IA) provides immediate intravascular reduction of autoantibody concentration and thus, may provide immediate benefits within hours. However, the effects typically last only 3 to 6 weeks. For sustained control of MG activity, concomitant immunosuppression must be initiated or modified. Absolute autoantibody levels do not typically correlate with disease severity.

Apheresis indications include myasthenic crisis, acute MG exacerbation (particularly in patients with bulbar or severe generalized symptoms) and pre-thymectomy clinical stabilization. In an RCT on thymectomy, TPE was used in 13% of patients to stabilize MG activity and to improve postoperative outcome (Wolfe, 2016). A meta-analysis also showed that TPE may reduce myasthenic crisis during the postoperative period in patients with severe MG but may only be beneficial in patients with milder disease (Reis, 2019). In therapy refractory patients, TPE or IA may represent an option for long-term management of MG (Sanders, 2016). Although no absolute consensus exists on the optimal schedule, studies have generally endorsed 3 to 6 treatments daily or on alternating days, which have equivalent efficacy compared to IVIG. Notably, treatment of plasma volumes below 1 TPV is effective in two thirds of patients with severe MG using TPE or IA (Köhler, 2011; Trikha, 2007). IVIG and TPE are generally regarded as equally effective in treating acute MG. A meta-analysis showed that TPE may shorten ventilator time while IVIG potentially shortens overall hospitalization (Ipe, 2021). A comparative effectiveness study using administrative data demonstrated IVIG to be more cost effective (Mandawat, 2010). Thus, IVIG may be preferable to TPE due to its ease in management. However, TPE was favored in patients with more severe respiratory impairment prior to initiating treatment. Accordingly, TPE was more effective in severe cases if initiated earlier after hospital admission (Mandawat, 2011). TPE may be more effective than IVIG in patients with MuSK- MG; however no comparative evidence currently exists (Ipe, 2021). TPE also appears to be effective in seronegative MG (Usami, 2019). IA or DFPP exhibited comparable efficacy to TPE.

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Technical notes

Volume treated: 1 to 1.5 TPV with TPE; 2 to 2.5 liters for tryptophan-IA (manufacturer's recommendation); up to 2.5 TPV with regenerative immune adsorbers

Replacement fluid: TPE: albumin; DFPP with plasma filters of small mean pore size distribution: albumin or FFP; IA: NA

Frequency: Acute attack/relapse or unstable disease activity: 3 to 6 treatments over 10 to 14 days; weekly to bi-weekly individually adjusted for chronic treatment

Duration and discontinuation/number of procedures

TPE or IA are appropriate options as fast acting interventions to acutely decrease MG activity. Actual number of procedures depends on the clinical scenario.

Keywords: myasthenia gravis, plasma exchange, immunoadsorption, thymectomy

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MYELOMA CAST NEPHROPATHY

Incidence: 1/100,000/year				
Procedure	**Category**		**Grade**	
TPE	II		2B	
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	5 (182)	1 (29)	10 (163)	NA

Description

Multiple myeloma (MM) is defined as the malignant proliferation of clonal plasma cells that secrete a monoclonal immunoglobulin (85%), excessive free light chains (FLCs, 13%) or more rarely, can be non-secretory. Kidney disease is present in up to 50% of patients at time of diagnosis and is recognized as a poor prognostic factor and associated with a higher tumor burden. Myeloma cast nephropathy (also known as myeloma kidney or light chain cast nephropathy) is the most common form of monoclonal immunoglobulin-mediated kidney disease. It results from the aggregation of excessive amounts of filtered free light chains with Tamm-Horsfall proteins (also known as uromodulin) in the distal tubule, causing intratubular obstruction of the lumen of the distal nephron. Stimulation of nuclear factor κB (NFκB) pathways by tubular toxicity of free light chains may also contribute to intratubular obstruction. As tubular obstruction increases, kidney damage progresses leading to interstitial nephritis and irreversible fibrosis. Concomitant hypercalcemia, hyperuricemia, dehydration, loop diuretics, intravenous contrast media, and non-steroidal anti-inflammatory agents can further potentiate the nephropathy. Myeloma cast nephropathy accounts for around 70% of dialysis-dependent kidney failure in MM and is a medical emergency requiring prompt intervention to rescue the kidneys from irreversible damage. The probability of cast nephropathy increases with the serum level of FLCs (usually >1000 mg/L) and the amount of its urinary excretion, and rarely occurs at a serum concentration <500 mg/L. The diagnosis is typically made clinically but kidney biopsy is the gold standard for diagnosis. Common non-light chain causes of acute kidney injury (AKI) include hypercalcemia, infections, hypovolemia, nephrotoxic drugs, and use of contrast media.

Current management/treatment

The treatment of elevated serum FLCs includes volume expansion with crystalloid solutions, chemotherapy (including alkylating agents (melphalan, cyclophosphamide), proteasome inhibitors (bortezomib, carfilzomib), or immunomodulatory drugs (thalidomide, lenalidomide)), corticosteroids, and in select cases, the addition of extracorporeal removal with TPE or high-cut off dialyzers (HCO-HD). Routine measurement of serum FLC is highly recommended to assess treatment efficacy. AKI in multiple myeloma is often multifactorial, and other supportive measures include discontinuing nephrotoxic medications, avoiding diuretics and intravenous contrast media, correction of hypercalcemia with calcitonin and bisphosphonate therapy, and managing hyperuricemia. Supportive care with hemodialysis or peritoneal dialysis is employed as needed.

Rationale for therapeutic apheresis

TPE has been used to acutely decrease FLCs, since early reduction in FLCs have been associated with better outcomes and overall survival. The impact of TPE in addition to chemotherapy on kidney outcomes in cast nephropathy is debated, and this should only be considered as an adjunct treatment to chemotherapy. An RCT 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 kidney function. Biopsy findings that indicated potential reversibility (e.g., absence of fibrosis of all affected glomeruli) to be an important predictor of success. This led to endorsement of TPE for myeloma kidney by the Scientific Advisors of the International Myeloma Foundation. The largest RCT of chemotherapy and supportive care (58 subjects receiving TPE and 39 controls) failed to demonstrate that 5 to 7 TPE procedures over 10 days substantially reduces a composite outcome of death, dialysis dependence, or estimated glomerular filtration rate of <30 mL/min/1.73m^2 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 principally because most of the enrolled patients were not proven to have cast nephropathy by kidney biopsy and FLC levels were not measured. Survival at 6 months, which was similar in the TPE and control groups, has been questioned as part of the composite outcome, as opposed to end points more specific to recovery of kidney function. For example, dialysis dependence in those who survived 6 months was 13% in TPE cases but 27% in controls; this difference was not statistically significant because of wide confidence intervals that suggest that the study was underpowered. Both the American Society of Nephrology Onco-Nephrology Forum and the Onconephrology Work Group of the Italian Society of Nephrology do not recommend plasma exchange as a treatment option for myeloma cast nephropathy. However, a Mayo Clinic CS restricted to patients with biopsy-proven cast nephropathy, showed that when TPE achieved a 50% reduction of FLC, then it was effective in reversing kidney failure and extending survival (Leung, 2008). Based on a report of 14 patients with presumed myeloma cast nephropathy treated with bortezomib and TPE, 12 had complete or partial response by 6 months (Burnette, 2011). One CT in 29 patients with myeloma and acute kidney injury showed a significant decrease of FLCs in patients treated with TPE compared to the bortezomib group and there was a significantly higher decrease of FLCs and longer survival in patients treated with 3 or more TPEs than patients treated with 2 TPEs (Premuzic, 2018). Thus, some believe that intensive TPE can improve kidney outcomes if applied immediately with concurrent chemotherapy until serum FLC levels have been substantially reduced. However, HCO-HD has been shown to remove more free light chains than TPE and a phase 2 trial of HCO-HD failed to show a benefit in patients with biopsy proven cast nephropathy that required dialysis (Hutchinson, 2019).

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Technical notes

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 to 1.5 TPV

Frequency: Daily or every other day

Replacement fluid: Albumin

Duration and discontinuation/number of procedures

CTs have employed TPE as a short-term adjunct to chemotherapy and fluid resuscitation over a period of 2 to 4 weeks. In some studies, a course of TPE (10-12 procedures over 2-3 weeks) may be repeated depending on the patient's clinical course. Serum FLCs should be measured to determine efficacy, and treatment frequency (daily versus every other day) should be dictated by the ability to achieve ≥50% reduction in FLCs.

Keywords: multiple myeloma, kidney/renal disease, apheresis, plasma exchange, plasmapheresis, cast nephropathy

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NEPHROGENIC SYSTEMIC FIBROSIS

Incidence: rare				
Procedure	**Category**		**Grade**	
ECP/TPE	III		2C	
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
ECP	0	0	5 (17)	4 (5)
TPE	0	0	5 (11)	2 (3)

Description

Nephrogenic systemic fibrosis (NSF) is a rare but potentially fatal systemic disorder thought to occur exclusively in patients with acute or chronic kidney disease (CKD) after the administration of specific types of gadolinium-based contrast agents (GBCAs). Not all GBCAs have the same risk of NSF. According to the classification of the American College of Radiology, group I agents have been associated with the highest risk for NSF, and include gadodiamide, gadopentetate dimeglumine, and gadoversetamide. Group II agents are deemed the lowest-risk group (gadobenate dimeglumine, gadoteridol, gadoterate meglumine, and gadobutrol). Group III consists of gadoxetate disodium and the now discontinued gadofosveset trisodium. In European publications, a similar distinction is made between linear and macrocyclic GBCA, with high NSF risk for linear GBCAs, and low risk for macrocyclic GBCAs. During 1997 to 2007 more than 500 cases of NSF were reported, which led to increased preventative measures, including screening kidney function prior to administration, avoidance of all GBCAs in at-risk patients, using lower-risk GBCAs, and decreasing the GBCA dose. The near elimination of new patients since 2008 indicates the success of these measures. Prior to these preventative measures, the reported incidence was 3% to 7% of patients with renal insufficiency largely receiving group I GBCAs. Risk factors include patients with GFR <30 mL/min/1.73 m^2, patients with current thrombosis or inflammation, and the use of higher or cumulative dose(s) of GBCAs. Additional factors associated include surgery, systemic infections, metabolic acidosis, high erythropoietin levels, exposure to lanthanum carbonate, and elevations in calcium, iron, zinc, copper, and phosphate. NSF has not been reported in those with a GFR >60 mL/min/1.73 m^2.

The onset of NSF usually occurs within 2 to 4 weeks after GBCA administration; however, the range can be from 2 days to 10 years. Initial clinical symptoms may be nonspecific and can include erythema, edema, and palpable warmth of the extremity associated with pain or pruritus. Additional findings include hair loss, gastroenteritis, conjunctivitis, bilateral pulmonary infiltrates, and fever. Over time, symmetric, bilateral, indurated plaques with a woody consistency develop (typically on the distal extremities, but also reported on the hands, forearms and trunk). Fibrosis results in joint contractures leading to wheelchair 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. Most patients experience a chronic and unremitting course with an overall mortality rate up to 30%. In a subgroup of patients with recovered kidney function, the disease can enter remission.

The pathophysiology of NSF remains unclear. Advanced kidney disease markedly prolongs the half-life of GBCAs as well as the circulating concentrations of endogenous metals (iron, copper, and zinc) which promotes the dissociation of gadolinium (Gd) from its chelating ligand. This dissociation can be further enhanced by the presence of metabolic acidosis. Once displaced, free Gd combines with endogenous ions such as phosphate to form complexes that can precipitate in tissues eliciting a pro-inflammatory and pro-fibrotic cytokine response leading to tissue infiltration by circulating CD34+ fibrocytes and collagen production. Gd may also directly stimulate fibroblasts. Clinical significance of retained or deposited Gd in the brain and nervous system, bones, and skin is currently under investigation.

Current management/treatment

There is no definite treatment besides reconstitution of kidney function. Thus, kidney transplant has been associated with cessation of progression and reversal in some patients. While hemodialysis has been shown to effectively remove circulating free Gd, it does not remove Gd chelates and the benefit of dialysis in prevention of NSF has not been established. Additional therapies tried have included IVIG, alefacept, pentoxifylline, imatinib mesylate, chelation therapy with sodium thiosulfate, TPE, and ECP; however, all are associated with inconsistent clinical improvement. Steroids and cyclophosphamide are generally associated with no improvement. Avoidance of higher risk GBCA (group I) administration has been recommended for patients with GFR <30 mL/min/1.73 m^2. In a systematic review and meta-analysis including 4931 patients with a GFR <30 mL/min/1.73 m^2, there were no cases of NSF after administration of group II GBCAs and the authors concluded that the potential diagnostic harm of withholding group II GBCA for indicated examinations may outweigh the risk of NSF in this population (Woolen, 2020).

Rationale for therapeutic apheresis

Due to the lack of an effective therapy and similarity between NSF and scleromyxedema, TPE has been applied. In the cases reported in the literature, patients demonstrated improvement including skin softening, increased range of motion (ROM), improved ambulation, and improvement from wheel-chair bound to walking. Additional reported changes include decreased swelling, pain, and paresthesias.

ECP has been applied to NSF because of similarities to symptoms of chronic graft versus host disease and scleromyxedema. In the reported cases, improvement includes skin softening, increased ROM, improved ambulation, and improvement from being wheel chair bound to walking. Additional reported changes include resolution of skin lesions and decreased pruritus.

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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: varies; TPE: 1 to 1.5 TPV	**Frequency:** ECP: Various schedules ranging from 2 in consecutive days every 2 to 4 weeks up to 5 procedures every other day (cycle) with increasing number of weeks between cycles (1 to 4) with 4 cycles composing a round; TPE: Various schedules ranging from daily for 5 treatments to twice per week for 10-14 treatments
Replacement fluid: ECP: NA; TPE: albumin	

Duration and discontinuation/number of procedures

Time to response has not been reported for most patients treated with TPE. Improvement of early symptoms in one patient reported to have occurred within 3 days of treatment initiation. Time to response with ECP ranged from 4 to 16 months.

Keywords: nephrogenic systemic fibrosis, plasma exchange, plasmapheresis, extracorporeal photopheresis, gadolinium

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NEUROMYELITIS OPTICA SPECTRUM DISORDER

Incidence: <1/100,000/year

Indication	Procedure	Category	Grade
Acute attack/relapse	TPE	II	1B
	IA	II	1C
Maintenance	TPE	III	2C

# reported patients: >300	Procedure	RCT	CT	CS	CR
Acute attack/relapse	TPE	1 (11)	5 (297)	>10 (>200)	NA
	IA	0	1 (61)	5 (60)	17 (21)
Maintenance	TPE	0	1 (30)	1 (7)	1 (2)

Description

Neuromyelitis optica (NMO) is a chronic inflammatory autoimmune disease of the central nervous system (CNS). Originally known as Devic's disease, NMO was long considered a variant of multiple sclerosis (MS). Discovery of pathogenic IgG autoantibodies to aquaporin 4 (AQP4), the most abundant water channel in the CNS, in >70% of patients led to differentiating NMO from MS. Due to varying clinical presentation, the term NMO spectrum disorder (NMOSD) was introduced. NMOSD occurs worldwide; however, significant regional differences in incidence and prevalence have been reported. Up to 40% of individuals with NMOSD who lack AQP4-IgG have IgG autoantibodies to myelin oligodendrocyte glycoprotein (MOG). MOG-IgG is also present in a subset of patients (mostly children) with acute disseminated encephalomyelitis (ADEM, see *separate fact sheet*). With the term MOG-associated disease (MOGAD) these patients are increasingly regarded as a separate entity in recent literature (Marignier, 2021). Rare cases of NMOSD were described in patients with sarcoidosis, infectious disease, connective tissue disorders and paraneoplastic neurological disorders. Core clinical characteristics and CNS magnetic resonance imaging must be considered for the diagnosis of NMOSD. Optic neuritis (ON), longitudinally extensive transverse myelitis (LETM), and area postrema syndrome (i.e., intractable hiccups, nausea, and vomiting) are cardinal symptoms of NMOSD in acute attacks or relapses, although some patients can also have brain or brainstem involvement. Unresolved classification issues for NMOSD exist, resulting both from the heterogeneous pathogenesis of NMOSD, the stratification based on autoantibody serology, and from the fact that some patients do not present with the full clinical syndrome. MOG-IgG-associated disorders (MOGAD) have been recognized as a distinct entity in recent years. Diagnostic criteria for seronegative or unknown AQP4-IgG status require presentation of above mentioned cardinal symptoms. At least two core clinical criteria must be present, one of which must be ON or LETM, imaging consistent with NMOSD, and no alternative explanation for symptoms. It is important to note, that ON alone can have many different underlying etiologies.

Autoantibodies against AQP4-IgG are 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. AQP4-IgG is usually absent in patients who are MOG-IgG-positive. Histopathology of inflammatory CNS lesions differs between patients who are MOG-IgG- and AQP4-IgG-positive. Binding of AQP4-IgG to astrocyte AQP4 channels triggers classical complement cascade activation, followed by granulocyte, eosinophil, and lymphocyte infiltration, culminating in injury first to astrocytes, then oligodendrocytes, demyelination, neuronal loss, and neurodegeneration. By contrast, primary demyelination is found in those with MOG-IgG. AQP4-IgG positive or seronegative NMOSD and MOGAD usually have a relapsing disease course with no major disease progression between attacks. Monophasic course is associated with younger age at disease onset and a 90% 5-year survival rate. Approximately 90% of patients with NMOSD have a 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. Pregnancies in patients with NMOSD are associated with increased disease activity and more severe disability postpartum.

Current management/treatment

Immunotherapy usually used to treat patients with MS is ineffective in patients with NMOSD and may even increase annualized relapse rates. The high risk of permanent disability mandates aggressive acute attack therapy and lifelong immunosuppression in most cases of AQP4-IgG positive NMOSD. High-dose intravenous corticosteroids (e.g., methylprednisolone, 1g daily for 3-5 days) followed by oral taper, and TPE or IA are the therapeutic mainstay for acute attacks of NMOSD as well as MOGAD. Azathioprine, mycophenolate mofetil (MMF), and less frequently methotrexate, calcineurin inhibitors, or cyclophosphamide are used for long-term stabilization. Several monoclonal antibodies are in use for the prevention of relapse in adults with AQP4-IgG positive NMOSD, namely rituximab, and tocilizumab, and recently approved eculizumab, inhibiting the C5 protein in the terminal part of the complement cascade; satralizumab, a monoclonal antibody which targets the IL-6 receptor; and inebilizumab, a monoclonal antibody that evokes antibody-dependent cellular cytolysis by binding to the B cell surface antigen CD19. Network meta-analysis estimated eculizumab to be the most effective of the latter 3 compounds, but long-term experience is not yet available (Wingerchuk, 2022). Individual decision making with highly specialized neurologists is mandatory.

Rationale for therapeutic apheresis

TPE or IA are recommended within 5 days from NMOSD relapse onset, when response to steroids is poor or absent. TPE can also be administered as first line therapy or simultaneously with steroids in severe cases, in particular when previous attacks have responded well to apheresis therapies but not to steroids. Prompt initiation of TPE is a strong predictor of beneficial outcome in severe attacks of NMOSD; for every day delayed in initiation of therapy, the odds of achieving complete remission were reduced by 6.3% (Bonnan, 2018; Kleiter, 2018). In serious transverse myelitis relapses, early TPE was linked to full recovery compared to high-dose steroids. Similarly, time from relapse onset to start of TPE was a robust predictor of complete remission. Moreover, 51% of patients treated with steroids for 5 days followed by TPE recovered pre-relapse baseline status, compared with 16.6% of patients treated only with steroids (Abboud, 2016).

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There is increasing experience using IA in addition to immunosuppressive therapy to treat patients with acute NMOSD with results essentially identical to TPE, and also in favor of first-line use (Faissner, 2016; Kleiter, 2016; Kleiter, 2018). The strongest predictors of complete remission were use of apheresis as first-line therapy, time from onset of attack to start of apheresis therapy, and presence of AQP4-IgG (Kleiter, 2018). Retrospective analyses have shown benefit of TPE as a maintenance treatment for the prevention of NMOSD relapse in select patients.

Technical notes

Volume treated: TPE: 1 to 1.5 TPV; IA: 2 to 2.5 liters for tryptophan-IA (manufacturer's recommendation); up to 2.5 TPV with regenerative immune adsorbers

Replacement fluid: Albumin

Frequency: Acute attack/relapse: daily or every other day, median of 5 treatments over 10 days, individually adjusted intervals for maintenance treatment

Duration and discontinuation/number of procedures

In the majority, 5 procedures were performed on average for acute exacerbation (range 2-10) (Abboud, 2016; Ipe, 2020). Maintenance TPE every 2 to 12 weeks performed for several years after taper of gradually declining TPE frequency showed varying degrees of improvement and reduction in the number of NMOSD exacerbations (Khatri, 2012; Visvanathan, 2021).

Keywords: neuromyelitis optica, neuromyelitis optica spectrum disorders, plasma exchange, immunoadsorption, optic neuritis

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N-METHYL-D-ASPARTATE RECEPTOR ANTIBODY ENCEPHALITIS

Incidence: rare				
Procedure	**Category**		**Grade**	
TPE/IA	I		1C	
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	0	3 (112)	>10 (>200)	NA

Description

N-methyl D-aspartate receptor (NMDAR) encephalitis is the most common form of autoimmune antibody-mediated encephalitis (Dalmau, 2018). This group of acute inflammatory brain disorders is characterized by prominent neuropsychiatric symptoms and is associated with antibodies against neuronal cell-surface proteins, ion channels, or receptors. NMDAR encephalitis is characterized by IgG antibodies targeting subunits (GluN1 and GluN2a) of the NMDAR. This disorder typically affects children and young adults and is frequently associated with ovarian teratoma. Young children typically present with insomnia, seizures, abnormal movements, or variable changes in behavior. Teenagers and adults often present with psychiatric symptoms, including agitation, hallucinations, delusions, and catatonia. The disease progresses in a period of days or weeks to include reduction of speech, memory deficit, orofacial and limb dyskinesias, seizures, decreased level of consciousness, and autonomic symptoms like excess salivation, hyperthermia, fluctuations of blood pressure, tachy- or bradycardia, or central hypoventilation. Occurrence as autoimmune sequelae after herpes simplex virus encephalitis must also be considered (Armangue, 2018). If autonomic dysfunction progresses (regardless of physiologic trigger), the disease can be fatal (mortality ∼4%). Definitive diagnosis is made by detection of NMDAR antibodies in the cerebrospinal fluid (CSF); in serum, false negative results are more frequent. Brain MRI is abnormal in ∼30% of patients. Delay in diagnosis is common as NMDAR encephalitis is often mistaken for psychosis or viral encephalitis. It has been postulated that immune-mediated cross-reactivity between the NMDAR GluN1 and GluN2a subunits and the SARS-CoV-2 nonstructural proteins 8 (NSP8) and 9 (NSP9) may induce molecular mimicry leading to production of IgG antibodies as a result of COVID-19 infection. A review of 8 cases of SARS-CoV-2-associated NMDAR encephalitis identifies clinical characteristics, diagnostic studies, and effective treatment modalities (Vasilevska, 2021).

Current management/treatment

Once diagnosed, immunotherapy should be initiated promptly. First-line therapy includes high-dose corticosteroids, IVIG, and/or TPE/IA, and a search for potential underlying tumor. Early initiation of immunotherapy is a strong predictor of favorable outcome after 12 months. In cases with associated tumor, optimal response to immunotherapy is contingent upon tumor removal. Approximately 50% of patients respond to these immunotherapies; the remaining 50% require additional therapies, such as rituximab or cyclophosphamide. In severe refractory cases, bortezomib is used to induce remission, and repeated pulsed corticosteroids to maintain remission (Scheibe, 2017; Wang, 2021). Approximately 80% of patients recover or improve at 24 months (∼50% within 4 weeks); in 20% of patients residual deficits remain. Recovery is gradual; relapses occur in 12% to 20% of cases. Patients who do not respond to treatment, or who have relapses, should be reassessed for presence of an underlying (still undetected or recurrent) teratoma. Disease activity appears to correlate with antibody levels; quantitation of autoantibodies is helpful in patient management and monitoring response to immunotherapy. Psychopharmacological treatment is often necessary for the management of psychiatric symptoms. A review of 30 patients with refractory NMDAR encephalitis (>86% showing symptoms of catatonia) demonstrated clinical improvement in 65% of cases with adjunct use of electroconvulsive therapy (Warren, 2019).

Rationale for therapeutic apheresis

TPE/IA removes the pathophysiologically relevant antibody, as an adjunct to immunotherapy suppressing active inflammation and antibody production. While some patients with NMDAR encephalitis do not respond to TPE alone, TPE/IA is one of the first-line treatment options (along with corticosteroids and IVIG) and is included in treatment recommendations from the German Network for Research on Autoimmune Encephalitis (https://en.generate-net.de/how-do-we-treat-autoimmune-encephalitis.html). The evidence for using TPE in NMDAR encephalitis is based on several CTs and CS (Aungsumart, 2019; Zhang, 2019; Zhang, 2021). Although NMDAR is an extracellular antibody, as in most autoimmune encephalitides, antibody production and inflammatory changes occur behind the blood-brain barrier, which may explain the slower response of TPE in this disorder, compared to systemic antibody-mediated disease (Dalmau, 2018). There is no broad consensus about the exact order to apply corticosteroids, IVIG, or TPE/IA, or when to initiate treatment with a combined multimodal approach. While systematic comparisons between the modalities are unavailable, studies suggest early initiation of TPE (or TPE followed by IVIG therapy) provides better outcomes. In addition, fewer patients demonstrated clinical improvement following corticosteroids as compared to corticosteroids immediately followed by TPE (DeSena, 2015). In a CT of 40 patients with NMDAR encephalitis refractory to corticosteroid and/or IVIG treatment, compared to the non-TPE group, the TPE group (19 patients) exhibited greater clinical improvement after 1 and 2 months following TPE (mean of 6 treatments/patient; $P<.05$), but after 6 and 12 months, there were no significant differences between groups. NMDAR antibody titers in CSF and/or serum were decreased or negative after course of TPE in 18 of 19 (95%) patients (Zhang, 2019).

IA was used in two CS mostly after an initial steroid pulse in 32 patients with antibody-associated encephalitis, including 16 with NMDAR encephalitis (Dogan-Onugoren, 2016; Köhler, 2015). After 5 to 10 IA treatments, clinical improvement was noted in most patients. Antibody titers were reduced by 97% in serum, and by 64% in CSF at early follow-up (Dogun-Onugoren, 2016). In a small, prospective, case-control study including 21 patients with antibody-associated encephalitis, TPE (5-12 treatments) was compared with IA (3-7 treatments; Heine, 2016). Both apheresis modalities showed equal efficacy with 60% to 70% of patients improving; slightly fewer side effects were noted with IA.

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Technical notes

Volume treated: TPE: 1 to 1.5 TPV; IA: 2 to 2.5 liters for tryptophan-IA (manufacturer's recommendation) or up to 2.5 TPV with regenerative immune adsorbers

Replacement fluid: Albumin

Frequency: 5 to 12 treatments with TPE or IA over 1 to 3 weeks with individually adjusted number of and intervals between treatments

Duration and discontinuation/number of procedures

In NMDAR encephalitis, IgG antibody needs to equilibrate between intravascular and extravascular spaces, as well as between plasma and CSF. Long periods of hospitalization may be required with occasional repetition of a series of TPE or IA before clinical improvement is noted.

Keywords: *N*-methyl-D-aspartate receptor, autoimmune encephalitis, plasma exchange, immunoadsorption

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PARANEOPLASTIC AUTOIMMUNE RETINOPATHIES

Incidence: 1/10,000 cancer patients/year

Indication	Procedure		Category	Grade
	TPE		III	2C
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
CAR/MAR	0	0	0	15 (16)
BDUMP	0	0	0	19 (22)

CAR= cancer-associated retinopathy; MAR= melanoma-associated retinopathy; BDUMP= bilateral diffuse uveal melanocytic proliferation.

Description

Paraneoplastic autoimmune retinopathy (PNAR), paraneoplastic ocular syndrome (POS), and ocular paraneoplastic syndromes (OPNS) are similar conditions subsumed under autoimmune retinopathy (AIR) which comprises paraneoplastic and non-paraneoplastic retinopathy. These conditions are characterized by inflammatory processes affecting the retina leading to photoreceptor dysfunction, visual field defects, scotoma, and acute or subacute vision loss often in association with the presence of anti-retinal antibodies. There are two main pathophysiological arms of paraneoplastic retinopathy: (1) autoimmune pathomechanism, characterized by cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), paraneoplastic vitelliform maculopathy (PVM), and paraneoplastic optic neuritis (PON), and (2) ectopic peptides, often caused by tumor-expressed growth factors (T-exGF), and characterized by bilateral diffuse uveal melanocytic proliferation (BDUMP; Przezdziecka-Dolyk, 2020). Paraneoplastic syndromes (PNS) have distinguishing characteristics which include: (1) syndrome is not a consequence of primary tumor or metastases; (2) diseased tissue is distant from the primary neoplasm; (3) more than one PNS may be associated with a single neoplasm; and (4) a variable temporal relationship often exists between the onset of the PNS and diagnosis of the primary tumor. Evidence suggests that paraneoplastic AIRs can be triggered by molecular mimicry between tumor antigens and retinal proteins (e.g., the most common retinal autoantigens in CAR are recoverin and α-enolase, in MAR: transducin-a and arrestin, and in BDUMP: recoverin and heat shock protein 70), whereby tumor cells with retinal photoreceptors expressing antigenic epitopes induce an immune response that interacts with retinal cells (including photoreceptors, ganglion cells, or bipolar cells). In vitro studies have shown that recoverin and α-enolase induce apoptosis of retinal cells. Despite this evidence, it is not clear why some patients with these antibodies develop AIR while others do not. Other evidence suggests that cellular rather than humoral immunity may play a central role in disease manifestation, and anti-retinal antibodies are an epiphenomenon related to disease without direct pathogenicity (Maeda, 2006).

Current management/treatment

CAR is most commonly associated with small cell lung CA (SCLC), and is also known to be linked with non-SCLC, gynecologic, and breast malignancies. Bilateral loss of vision occurs over several months (due to both rod and cone dysfunction) and visual symptoms precede malignancy diagnosis in ∼50% of cases. MAR is associated with cutaneous, choroidal, and intestinal melanomas with clinical features including sudden onset of night blindness, visual field defects, bilateral shimmering photophobia, and reduction in b-wave amplitude in electroretinography (ERG), with a mean latent period of 3 to 4 years between diagnosis of the primary lesion and onset of MAR (Keltner, 2001). BDUMP has been characterized by five cardinal ophthalmologic signs: (1) multifocal red subretinal patches, (2) hyperfluorescence pattern, (3) diffuse thickening of the uveal tract, (4) exudative retinal detachment, and (5) rapid cataract formation (Gass, 1990). BDUMP is most commonly associated with gynecologic, lung, and pancreatic carcinomas which trigger uveal melanocyte proliferation due to molecular mimicry, in addition to the presence of "cultured melanocytic elongation and proliferation (CMEP) factor" in the serum of patients with BDUMP (Miles, 2012).

In CAR, combinations of systemic corticosteroids, TPE, and IVIG have been found to be beneficial (Murphy, 1997). In 6 of 6 patients with CAR, the combination of moderate dose prednisone (0.5-0.75 mg/kg/day), and daily cyclosporine and azathioprine showed significant improvement in visual acuity and fields (Ferreyra, 2009). Other treatment options for CAR include: IV or intravitreal injections of corticosteroids, mycophenolate, rituximab (Dy, 2013), and alemtuzumab (Espandar, 2007).

In MAR, therapeutic options often focus on cytoreductive treatment (surgery, chemotherapy, etc.) in combination with systemic corticosteroids, IVIG, and/or TPE. Intravitreal long-acting fluocinolone acetonide implants appear to be effective in controlling MAR without the systemic effects of immunosuppressive therapies (Karatsai, 2019).

In BDUMP, treatment options include: management of primary malignancy, ocular radiation, local or systemic corticosteroids, intraocular and/or cataract surgery, intravitreal triamcinolone acetonide (bevacizumab, ranibizumab, or other anti-VEGF antibody therapy), photodynamic therapy, as well as IVIG and TPE treatment.

Rationale for therapeutic apheresis

While published literature is limited to small CS or CRs, there is increasing evidence TPE has a therapeutic role in paraneoplastic retinopathy (especially BDUMP). The observation that a CMEP factor from the IgG fraction of serum of patients with BDUMP has been shown to trigger melanocytic proliferation (Miles, 2012), and that only serum obtained prior to TPE can induce melanocytic lesions (Jansen, 2015), suggests a theoretical efficacy of TPE in this type of PNAR. A comprehensive review of treatments for BDUMP evaluated 68 cases in which multiple primary treatment options were instituted showing ∼33% overall improvement; of this cohort, 7 of 9 (78%) patients who underwent primary tumor therapy and TPE showed definitive clinical improvement (Moreno, 2017). Other CRs of the use of TPE in patients with BDUMP have shown improvement in visual acuity, visual fields, and serous retinal detachment (Mets, 2011; Jaben, 2011; Pulido, 2013; Jansen, 2015). Treatment with TPE appears to be more successful if started early (within 3 months of diagnosis). In CAR, the combination of TPE and CS therapy ± other immunomodulatory therapies yields better outcomes (Querques, 2010; Liu, 2015). In the largest CS on patients diagnosed with MAR, 3 of 62 pts received TPE treatment; 2 of 3 patients received combination of oral or IV corticosteroids and TPE, with one patient showing mild improvement in Goldmann visual fields and ERG, and the other showing significant improvement in visual acuity and fields (Keltner, 2001).

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Technical notes

Early diagnosis of paraneoplastic retinopathy may allow for more rapid evaluation and eventual treatment of associated malignancy as PNAR symptoms often precede evidence of underlying cancer. TPE for 5 to 7 procedures (every other day or 2-3 times/week), occasionally up to 12 to 18 treatments as initial therapy, with maintenance therapy (1-4 TPE treatments/month as needed) has been utilized depending on clinical response (Mets, 2011; Antaki, 2022), with subsequent TPE courses employed if relapse occurs (Pulido, 2013).

Volume treated: 1 to 1.5 TPV

Frequency: Every other day to weekly

Replacement fluid: Albumin

Duration and discontinuation/number of procedures

Different TPE protocols have been described ranging from every other day (for 1 week) up to 2 to 3 times/week (for ≥7 months) depending on clinical response (Miles, 2012; Jansen, 2015), with additional TPE treatment as needed.

Keywords: paraneoplastic retinopathy, autoimmune retinopathy, cancer-associated retinopathy, melanoma-associated retinopathy, bilateral diffuse uveal melanocytic proliferation, plasma exchange, plasmapheresis

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PARANEOPLASTIC NEUROLOGICAL SYNDROMES

Incidence: 4 to 9/1,000,000 person years

Procedure	Category		Grade	
TPE/IA	III		2C	
# reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
TPE	0	2 (35)	15 (111)	NA
IA	0	0	1 (13)	1 (1)

Description

Paraneoplastic neurologic syndromes (PNS) are defined as neurologic disorders that (1) can affect any part of the nervous system, (2) occur in association with cancer, and (3) have an immune-mediate pathogenesis (Graus, 2021). Classical PNS manifestations are cerebellar degeneration, encephalomyelitis, limbic encephalitis, opsoclonus-myoclonus syndrome (which is the most common pediatric PNS), sensory neuronopathy, chronic gastrointestinal pseudo-obstruction, and Lambert-Eaton myasthenic syndrome. The onconeural antibodies (ON-Abs) target antigens expressed by both the tumor and the nervous system. Antibodies may recognize intracellular antigens [e.g., Hu, CV2/CRMP5 (collapsin response mediator protein 5), Yo, Tr, and amphiphysin]. Since many ON-Abs are directed against intracellular antigens, which are not directly accessible to the antibodies, it is presumed that the main pathogenic effect is carried out by cytotoxic T cell mediated immune reactions, resulting in neuronal cell death. Many additional antibodies are against cell surface or synaptic proteins (e.g., NMDAR, VGKC, GABA, LGI1, and AMPAR). PNS is rare, occurring in 0.1% to 1% of patients with cancer. Specific forms of PNS are covered separately (see Lambert-Eaton myasthenic syndrome, Myasthenia gravis, *N*-methyl-D-aspartate receptor antibody encephalitis, Paraneoplastic autoimmune retinopathies, Stiff-person syndrome, and Voltage-gated potassium channel antibody related diseases). Neurologic disorders due to paraproteins and checkpoint inhibitors are also covered separately (see Chronic acquired demyelinating polyneuropathies and Immune checkpoint inhibitor toxicity).

The tumors most commonly associated with PNS are those that express neuroendocrine proteins [small cell lung cancer (SCLC), breast, ovary, or other gynecological malignancies], tumors that contain nervous tissue (teratomas), and tumors that affect organs with immunoregulatory functions (thymoma). PNS often precede detection of the underlying cancer; patients in whom PNS is strongly suspected but no cancer has been identified should undergo periodic cancer screening for at least 5 years. PNS has been observed following use of immune checkpoint inhibitors (see *separate fact sheet*).

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 the underlying cancer. Finally, tumor screening guided by 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 (Giometto, 2010). It has been reported that 60% of PNS of the central nervous system and <20% of those affecting the peripheral nervous system are associated with these antibodies. However, antibody titers have not been shown to clearly correlate with symptoms.

Current management/treatment

Treatment of PNS includes anti-tumor and immunosuppressive therapy. Prompt initiation of anti-tumor therapy upon diagnosis can stabilize symptoms. In the appropriate clinical setting, immunosuppressive treatment should not be delayed for antibody confirmation. Historically, most patients have been treated with corticosteroids, followed by TPE/IA and/or IVIG, and with additional therapies such as rituximab and/or cyclophosphamide also used. Several cases in the literature have been treated with IVIG without TPE/IA. Aggressive immunosuppression early in the course is recommended in patients who are identified prior to a tumor diagnosis. The safety of attempting apheresis in a particular individual with behavioral or movement disorders should be considered (Ciano-Peterson, 2022).

Rationale for therapeutic apheresis

The association of syndromes with specific cerebrospinal fluid and serum antibodies has led to the use of 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 progressive syndrome, aggressive immunosuppression plus TPE/IA may be reasonable in an attempt to halt the process. Patients with ON-Abs to extracellular antigens are more likely to respond to immunosuppressive therapies. A CS of 13 patients with opsoclonus-myoclonus syndrome (OMS) or subacute cerebellar degeneration were treated with staphylococcal protein A column IA (Batchelor, 1998). There were 3 complete and 3 partial neurological remissions; all subsequently relapsed. Although the exact mechanism of action of protein A column IA is not well understood, data suggest it results in a reduction of circulating IgG antibodies and immune complexes and an increase in natural killer cell activity.

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Technical notes

Volume treated: TPE: 1 to 1.5 TPV; IA: 2 to 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 to 6 procedures over 1 to 2 weeks. In one reported clinical study, patients were treated with protein A IA twice weekly for 3 weeks (Batchelor, 1998).

Keywords: paraneoplastic neurologic syndromes, onconeural antibodies, cerebellar degeneration, limbic encephalitis, paraneoplastic encephalomyelitis, opsoclonus-myoclonus syndrome, plasma exchange, and immunoadsorption.

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PEDIATRIC AUTOIMMUNE NEUROPSYCHIATRIC DISORDERS

Incidence: PANDAS/PANS: rare; Sydenham's chorea: 10% to 50% of acute rheumatic fever patients

Indication	Procedure		Category	Grade
PANDAS/PANS, exacerbation	TPE		II	1B
Sydenham's chorea, severe	TPE		III	2B
# reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
PANDAS/PANS	1 (29)	0	3 (76)	10 (10)
Sydenham's chorea	1 (18)	0	0	2 (2)

PANDAS = pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS = pediatric acute-onset neuropsychiatric syndrome.

Description

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), pediatric acute-onset neuropsychiatric syndrome (PANS), and Sydenham's chorea (SC) are post-infectious autoimmune neuropsychiatric disorders associated with group-A beta-hemolytic streptococcus (GABHS) infection. SC, a neuropsychiatric manifestation of acute rheumatic fever (ARF), occurs in an estimated 10% to 50% of patients with ARF, is self-limiting and typically resolves after 3 to 18 months but recurrence may be more common than previously appreciated (up to 40%). The major clinical manifestations include involuntary choreoathetoid movements, hypotonia, and emotional lability. Neuropsychiatric symptoms in the absence of ARF may represent PANDAS/PANS. PANDAS was first described in 50 children (Swedo, 1998) and is defined by the following diagnostic criteria: (1) presence of obsessive-compulsive disorder (OCD) and/or a tic disorder, (2) prepubertal onset, (3) episodic (relapsing-remitting) course, (4) temporal association of symptoms with GABHS infection, and (5) association with neurological abnormalities. Broader PANS diagnostic criteria were later proposed to improve cohort standardization (Chang, 2015), adding an "abrupt" qualifier to OCD or food-restriction symptom onset (within 48 h) and removing the diagnostic requirements of tic disorders, pre-pubertal age, and GABHS association. Additionally, exclusion of neurologic and medical disorders (i.e., SC, systemic lupus erythematous, Tourette's syndrome) are explicitly stated. The major clinical manifestations of PANDAS/PANS include anxiety, obsessions, compulsions, mood lability, depression, irritability, aggression, severely oppositional behaviors, developmental regression, sensory or motor difficulties, and somatic signs and symptoms including sleep disturbances, enuresis, or urinary frequency. The peak age of onset for PANDAS and SC are 6 to 7 years and 8 to 9 years, respectively. No laboratory tests are specific for the diagnosis and differentiation of PANDAS/PANS and SC. Evidence of current or preceding GABHS infection through throat culture and/or an elevated or increasing antistreptococcal antibody titer [e.g., anti-streptolysin O (ASO)] supports the diagnosis of both. Elevated levels of anti-neuronal antibodies and/or anti-basal ganglia antibodies and magnetic resonance imaging findings of striatal enlargement in the basal ganglia, especially in caudate, putamen, and globus pallidus, have been reported in PANDAS/PANS and SC.

Current management/treatment

Initial treatments for PANDAS/PANS include cognitive behavioral therapy and/or psychotropic medications. Prompt antibiotic administration is indicated in patients with tonsillo-pharyngitis and a positive GABHS throat culture for the prevention of ARF and may reduce OCD symptoms in PANDAS/PANS cases. In one double blind RCT, penicillin and azithromycin prophylaxis were found to be effective in decreasing streptococcal infections and neuropsychiatric symptom exacerbations in children with PANDAS (Snider, 2005). Another double-blind RCT in PANS adolescents identified a reduction in OCD and tic symptoms with azithromycin treatment, but not other neuropsychiatric outcomes (Murphy, 2017). In an observational study, corticosteroid use was found to be associated with reduction in symptom duration (Brown, 2017). Both IVIG and TPE use have been associated with neuropsychiatric improvement in an RCT and CTs (Perlmutter, 1999; Latimer, 2015; Williams, 2016). Tonsillectomy has been reported in CR and CS as a treatment option in patients with PANDAS/PANS but has not been supported in larger studies (Murphy, 2013). The severe form of SC is treated with diazepam, valproic acid, carbamazepine, or haloperidol. If these fail, corticosteroids, IVIG, and TPE have been reported. Unlike in PANDAS/PANS, children with SC require long-term penicillin prophylaxis to reduce the risk of rheumatic carditis.

Rationale for therapeutic apheresis

Given the association with anti-neuronal antibodies in the pathogenesis, antibody removal by TPE may be effective. An RCT of IVIG compared to TPE on 29 children with PANDAS showed that both therapies at one-month post treatment produced striking improvements in OCD, with mean improvement of 45% and 58%, respectively, as well as improvement in anxiety and overall function (Perlmutter, 1999). This effect appeared to be sustained on one-year follow up. The TPE group appeared to have greater tic symptom relief than did the IVIG group. In a large retrospective CS of TPE in 35 patients with PANDAS, 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 (Latimer, 2015). In a CS of 16 older adolescent and adult patients with PANDAS/PANS receiving courses of 5 to 7 TPE, 4 of 7 patients with follow-up data reported symptomatic improvement within 10 days of treatment (Prus, 2021). Responders received additional TPE courses for subsequent symptomatic episodes. 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 (Garvey, 2005).

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Technical notes

Volume treated: 1 to 1.5 TPV

Frequency: Daily or every other day

Replacement fluid: Albumin

Duration and discontinuation/number of procedures

Three to 6 procedures performed over 1 to 2 weeks. There is limited data on benefit of repeated TPE treatment courses.

Keywords: PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, Sydenham's chorea, group-A beta-hemolytic streptococcus, plasma exchange

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PEMPHIGUS VULGARIS

Incidence: 12/100,000/year (United States)

Indication	Procedure		Category	Grade
Severe	TPE		III	2B
	IA/ECP/DFFP		III	2C
# reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
TPE	1 (40)	0	8 (87)	NA
IA	0	1 (6)	20 (35)	5 (5)
ECP	0	0	1 (4)	8 (12)
DFFP	0	0	1 (17)	0

Description

Pemphigus vulgaris is a rare, potentially fatal, autoimmune mucocutaneous blistering disease. The typical age of onset is 45 to 65 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 burns. The pathology of pemphigus vulgaris is characterized by the in vivo deposition of autoantibody directed against 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. Desmoglein1 and 3 autoreactive CD4 + T-cells are detected in patients. There is an association with HLA alleles DRB1*04:02 and DQB1*05:03. Paraneoplastic pemphigus represents 3% to 5% of cases and is most commonly associated with hematologic malignancies, including lymphoma, leukemia, and Castleman disease.

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% to100% to 30%. However, long-term administration of high dose corticosteroids can be associated with severe adverse effects. The addition of rituximab has resulted in long term remission for 90% of patients with moderate to severe disease and allows for rapid tapering of corticosteroids. Other recommended therapeutic options include other immunosuppressant agents (azathioprine or mycophenolate mofetil), IA, and IVIG.

Rationale for therapeutic apheresis

The rationale for using apheresis in pemphigus vulgaris treatment is removal of circulating pathogenic autoantibodies. TPE has been utilized in patients with severe symptoms who either received high doses of conventional agents and/or had an aggressive and rapidly progressive disease or treatment resistant. Current recommendations conclude that the risk to benefit ratio argues against the use of TPE in pemphigus vulgaris (Schmidt, 2019). There are CRs describing the use of TPE in paraneoplastic pemphigus; results have been mixed.

IA has a more favorable risk/benefit profile and has been promoted in Europe with increasing number of patients treated and reported clinical responses. A significant reduction in the the level of antibodies and improvement of disease status has been reported with IA (Hübner, 2018). An RCT examining the use of adjuvant IA in pemphigus has completed recruitment but results are not yet published (DRKS00000566).

ECP (Knobler, 2021) and DFPP (Liu, 2021) have only been described in CS and CRs to date as adjunctive therapy to immunosuppression. CAR-T cell therapy is anticipated as a future option for treating this severe disease specifically (Schmidt, 2019).

Technical notes

TPE protocols vary widely in volume treated (400-4000 mL) and have been based on observed clinical response after each treatment. Autoantibody levels rebound within 1 to 2 weeks after TPE discontinuation, thus corticosteroids are used for continued immunosuppressive therapy. Clinical response with ECP has been observed after 2 to 7 cycles (two daily procedures per month). The total number of cycles has varied from 2 to 51. In one report, 100% clinical response with decreased autoantibody titer was reported after follow-up of 4 to 51 months. The disease was controlled in most patients; steroids could be tapered but were rarely discontinued.

Volume treated: TPE/DFPP: 1 to 1.5 TPV; IA: 2 to 4 TBV; ECP: varies

Frequency: IA: First week 3 daily, then weekly and tapering; TPE: daily or every other day; ECP: One cycle every 2 or 4 weeks

Replacement fluid: TPE: albumin, plasma; IA/ECP/DFPP: NA

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Duration and discontinuation/number of procedures

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

Keywords: pemphigus vulgaris, immunoadsorption, plasma exchange, extracorporeal photopheresis

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PERIPHERAL VASCULAR DISEASES

Prevalence: ~5% at 40 to 44 years and ~12% at 70 to 74 years

Procedure	Category		Grade	
LA*	II		1B	
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Acute/short course of treatment**	0	1 (87)	>10 (>200)	NA
Chronic treatment	1 (42)	0	2 (40)	0

*LA in this setting reflects a variety of methods including HELP-apheresis, dextran-sulfate adsorption, DFPP, and others; **includes some patients that transitioned to chronic treatment after an initial short course.

Description

Peripheral vascular disease (PVD) can be arterial [also known as peripheral arterial disease (PAD) or peripheral artery occlusive disease (PAOD)], venous, or mixed. PAD is a condition with narrowing and obstruction of the arteries that supply the legs or arms. Risk factors include smoking, diabetes mellitus, dyslipidemia, hypertension, coronary artery disease, kidney disease on hemodialysis, and cerebrovascular disease. PVD is a strong risk factor for cardiovascular disease. This fact sheet addresses the acute and chronic use of apheresis in PAD, critical limb ischemia, and ischemic diabetic foot syndrome (see Lipoprotein (a) hyperlipoproteinemia, Familial hypercholesterolemia, and Vasculitis, other; these may also have a PVD component).

Clinical presentation of PAD may be asymptomatic or exhibit claudication (pain, achiness, fatigue, burning, or discomfort in the affected muscles triggered by walking or exercise and relieved 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 PAD is made through the ankle brachial pressure index (ABPI/ABI), followed by a lower limb Doppler ultrasound examination for site and extent of atherosclerosis. In addition, angiography, computerized tomography, and magnetic resonance imaging are also used. Several classification systems are used to categorize the severity of PAD that include presentation and symptoms, anatomic distribution, and clinical factors such as presence of wounds and infection (Hardman, 2014). PVD classification by the Fontaine system is stage I = asymptomatic, incomplete vessel obstruction, stage II = mild claudication pain in the limb with IIa at a distance >200 m and IIb at a distance <200 m, stage III = rest pain, mostly in feet, and stage IV = necrosis and/or gangrene of the limb.

Current management/treatment

PVD management guidelines recommend smoking cessation, structured exercise therapy, lipid-lowering therapy, antihypertensives, diabetes management, and antithrombotics. Cilostazol and pentoxifylline have been used for claudication. In severe cases, angioplasty and stent placement of the peripheral arteries or peripheral artery bypass surgery of the leg can be performed.

Rationale for therapeutic apheresis

LA can decrease LDL cholesterol, oxidized LDL, lipoprotein(a), C-reactive protein (CRP), and fibrinogen transiently. One RCT with chronic LA in men with primary hypercholesterolemia and extensive coronary atherosclerosis, randomized patients to receive either biweekly LA plus simvastatin ($n = 21$) or simvastatin ($n = 21$) only (Kroon, 1996). The LA plus simvastatin arm showed decreases in levels of apolipoprotein B, total cholesterol, and lipoprotein(a) levels, decreased intima-media thickness of the carotid artery, and a statistically significant trend in decreased stenosis in the lower limbs as compared to the control arm. A study comparing 2 years before to 2 years after starting LA observed a significant decreased in major adverse cardiovascular events (MACE) and cerebrovascular events (Berent, 2019). Another study comparing 1 year before to 2 years after starting LA, found improvements in a number of parameters, including need for revascularization procedures (Poller, 2017).

Several studies have reported clinical benefit after a short series of LA procedures, though long term follow-up is lacking in several studies and some patients went on to continue chronic series of treatments. A retrospective CT compared 62 patients with below knee endovascular therapy (BK-EVT) only versus 25 with BK-EVT plus LA, and found lower major adverse limb events (amputation and re-intervention) in the LA group (Ohtake, 2016). A study in 28 patients with PVD treated with 10 sessions of LA (2 times per week for 5 weeks) with follow-up after 3 months, showed overall improvement including decreases of 82% in foot chillness or numbness, 54% in intermittent claudication, and 14% in foot ulcers, respectively (Kobayashi, 2005). A study of 31 patients demonstrated improvement in physiological parameters such as ankle brachial index (ABI), maximum tolerated walking distance (MTWD), and clinical symptoms treated with an average of 9.6±0.8 LA procedures (Tsuchida, 2006). One study showed a significant enhancement in tissue blood flow of both the head and lower limbs after 5 LA treatments in 5 weeks in 18 patients (Ebihara, 2007). Similarly, clinical improvement was observed in 10 out of 19 hemodialysis patients with PVD and treated with 10 sessions of LA (Tsurumi-Ikeya, 2010). In the patients who responded, LA resulted in a short-term decrease in total cholesterol and LDL cholesterol and a long-term reduction of the circulating levels of oxidized LDL, CRP, and fibrinogen. A series of 28 patient treated with a median of 15 procedures (range 6-86) observed a 53.6% 1 year amputation free survival rate and 71.4% complete wound healing within 1 month, however 30.4% had relapse with a new lesion after treatment was stopped (Solignac, 2022).

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Technical notes

In this context, a variety of LA techniques, including HELP-apheresis, dextran-sulfate adsorption, DFPP, rheopheresis, and others have been used. Angiotensin converting enzyme (ACE) inhibitors are contraindicated in patients undergoing LA. The columns function as a surface for plasma kallikrein generation which, in turn, converts bradykininogen to bradykinin. Kininase II inactivation of bradykinin is prevented by ACE inhibition resulting in unopposed bradykinin effect, hypotension and flushing. This is not seen with the HELP system.

Volume treated: 3000 to 5000 mL of plasma

Frequency: Short term: variable ~1 to 2/week; chronic: 1/1 to 2 weeks

Replacement fluid: NA

Duration and discontinuation/number of procedures

The number of procedures has varied between studies. In the acute or short term treatment studies, the treatment course often starts with 1 to 2 procedures/week then transitions to a procedure every 1 to 2 weeks phase. The number of procedures has ranged from 5 to 10 in 5 weeks to 10 in 10 weeks, though longer and shorter series have been reported. For chronic treatment, patients typically receive a procedure every 1 to 2 weeks.

Keywords: peripheral vascular disease, peripheral artery disease, LDL apheresis

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PHYTANIC ACID STORAGE DISEASE

Incidence: rare

Procedure	Category		Grade	
TPE/LA	II		2C	
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
TPE	0	0	2 (12)	13 (14)
LA	0	0	2 (8)	2 (2)

Description

Phytanic acid storage disease (Refsum's disease, also known as heredopathia atactica polyneuritiformis) is an autosomal recessive major peroxisomal biogenesis disorder first described by Sigvald Refsum, a Norwegian neurologist, in 1946. Peroxisomes are multiple membrane-bound intracellular organelles involved in catalyzing various functions in cellular metabolism and biosynthesis. Over 90% of 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. Fewer than 10% have a deficiency of type 2 peroxisomal targeting signal (PTS2) receptor. Clinical consequences are largely neurological including retinitis pigmentosa, peripheral neuropathy, cerebellar ataxia, sensorineural deafness, and anosmia. Other manifestations include skeletal abnormalities, arrhythmias, and ichthyosis. 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 PA 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 heart involvement may experience arrhythmias, which could be fatal or prompt heart 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 ichthyosis. Care is taken to maintain overall general nutrition and caloric intake to avoid rapid weight loss, which can precipitate a 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. PA levels must be closely monitored during pregnancy due to increase in the third trimester with worsening of symptoms.

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 mmol/L. Symptomatic levels of PA range from 700 to 8,000 mmol/L. Several small CS and isolated CRs have described clinical improvements in patient signs and symptoms with TPE in conjunction with dietary control. TPE has been found to improve polyneuropathy, ichthyosis, 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, due to mobilization of PA stored in adipose tissue. CRs and CS 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 LA using double-membrane filtration or dextran sulfate plasma perfusion LA has been reported in two CRs and two CS totaling 8 patients (Straube, 2003; Zolotov, 2012). In LA, the efficiency of PA removal was found to be equivalent to TPE but with less IgG loss. In one CS, patients were treated for as long as 13 years with weekly to biweekly LA resulting in lowering of PA levels, improvement in nerve conduction studies, and stabilization of vision (Zolotov, 2012).

Technical notes

Although approaches to therapeutic apheresis vary, a typical course consists of 1 to 2 TPE per week for several weeks or months. In some cases, maintenance TPE continues with tapering frequency over the course of a year. When LA has been used for chronic therapy, treatments have been weekly to every other week.

Volume treated: TPE, LA: 1 to 1.5 TPV

Frequency: Daily or every other day for acute exacerbation; variable (e.g., weekly or biweekly, mainly guided by major symptoms) for chronic therapy

Replacement fluid: TPE: albumin; LA: NA

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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.

Keywords: phytanic acid storage disease, Refsum's disease, heredopathia atactica polyneuritiformis, plasma exchange, selective removal, lipoprotein apheresis

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POST-TRANSFUSION PURPURA

Incidence: 2/100,000 transfusions

Procedure	Category		Grade	
TPE	III		2C	
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	1 (3)	16 (24)

Description

Post-transfusion purpura (PTP) is a rare and delayed transfusion-related complication characterized by severe and abrupt onset of profound thrombocytopenia (platelet count $<10 \times 10^9$/L) 5 to 10 days after transfusion of any platelet-containing blood component. It commonly following RBC transfusion and can present with widespread purpura, bleeding from mucous membranes, and in severe cases intracranial hemorrhage and death. PTP occurs most frequently 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 thrombotic thrombocytopenic purpura (TTP), drug-induced thrombocytopenia (including heparin-induced thrombocytopenia and vaccine-induced immune thrombotic thrombocytopenia), immune thrombocytopenia (ITP), sepsis, and disseminated intravascular coagulation (DIC). The pathogenesis of PTP remains incompletely understood; what is apparent is that there is destruction of 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 that bind to the patient's 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 associated with PTP can be up to 5% to 10% due to fatal hemorrhage. 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), resulting in 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. High doses of corticosteroids are used but appear not to change the disease course. There is a single CR of response to splenectomy in a patient who was not responsive to IVIG, steroids, or TPE (Cunningham, 1989).

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 CRs, 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. ACD-A may be preferred for anticoagulation due to increased bleeding risk associated with heparin in the setting of profound thrombocytopenia. Typically, the replacement fluid is albumin to avoid further exposure to HPA-1a antigen that may still be present in plasma. However, in bleeding patients, plasma may be given towards the end of procedure to maintain clotting factor levels.

Volume treated: 1 to 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 clinically significant bleeding improves.

Keywords: post-transfusion purpura, plasma exchange, intravenous immunoglobulin, HPA-1 antigen, platelet antibody

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PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY ASSOCIATED WITH NATALIZUMAB

Incidence: ~4/1,000 exposed patients/yr

Procedure	Category		Grade	
TPE	III		1C	
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	0	0	8 (304)	NA

Description

Disease modifying therapies (DMT) have been widely and successfully implemented in routine care for multiple sclerosis (MS) to prevent disease progression and decrease relapse rate. The first reported case of DMT-associated progressive multifocal leukoencephalopathy (PML) dates back to 2005, and was associated with a combination of natalizumab (NTZ) and interferon beta-1. NTZ remains the most frequent DMT associated with PML (NTZ-PML). Cases of PML have been also reported as a complication of different DMT, namely fingolimod, dimethyl fumarate, alemtuzumab, and ocrelizumab.

PML is a rare and often fatal neurological disorder occurring in immunocompromised patients. It is due to reactivation of the JC polyoma virus (JCV) or human polyomavirus 2, which causes lytic infection of oligodendrocytes and astrocytes in the CNS. In healthy individuals, JCV establishes an asymptomatic persistent infection in the kidney. Serum antibodies against JCV are present in approximately 50% to 90% of the general population. In patients with prolonged and profound compromise of cellular immunity, JCV can reactivate and undergo sequential genomic rearrangements. This intra-host viral evolution allows to cause lytic infection of CNS glial cells resulting in PML. Since PML is a white matter disease of the brain, the clinical presentation depends on the anatomic location of lesions. The initial clinical presentation of PML may include a large variety of neurological symptoms, including cognitive dysfunction, hemianopsia, aphasia, motor or sensory dysfunction, seizures, and ataxia, often with subacute progression. The optic nerve or spinal cord, typically affected by MS relapse, are not involved.

NTZ is a humanized monoclonal antibody directed against the α4 subunit of α4β1 and α4β7 integrins, which are localized on the surface of circulating mononuclear cells. NTZ inhibits the binding of the integrins to the endothelial cells subsequently limiting the passage of lymphocytes through the blood-brain barrier. NTZ is a highly effective and well-tolerated treatment for relapsing-remitting MS, but if treatment is discontinued, clinical disease activity returns in 9% to 80% of patients after 4 to 7 months.

Current management/treatment

Extended interval dosing (EID) has become a strategy to reduce the incidence of NTZ-PML. Immune reconstitution is the only intervention with demonstrated efficacy for PML. For NTZ-PML, management includes discontinuation of the drug (temporary or permanent) and consideration for initiation of TPE to accelerate clearance, especially if the drug is recently infused. Both will increase the number and function of leukocytes migrating to the CNS.

Rapid immune reconstitution may precipitate an extreme immune response called immune reconstitution inflammatory syndrome (IRIS), which is associated with neurological status deterioration, often life threatening. IRIS usually develops 2 to 6 weeks after TPE (vs. 3 months after drug discontinuation) in almost all patients with NTZ-PML. IRIS stems from massive influx of lymphocytes into the CNS following the antibody's clearance leading to renewed immune surveillance and increased inflammation. Abrupt worsening of neurologic symptoms in patients treated with TPE therefore most likely represents IRIS and not a worsening disease course. The recommended treatment of IRIS is high-dose corticosteroids and not TPE. Given the possible involvement of chemokine receptor 5-postive (CCR5+) T cells in IRIS pathophysiology, use of maraviroc, a CCR5 antagonist was used for IRIS prevention in post-TPE NTZ-PML but did not demonstrate reproducible benefit (Bernard-Valnet, 2022). Immunoactivation with G-CSF during PML was beneficial in a case series of 17 patients with NTZ-PML with subsequent IRIS without worsening MS (Stefoski, 2019).

Rationale for therapeutic apheresis

NTZ's long duration of action delays immune reconstitution for several months. Unrestrained PML is often lethal in the 3 months after symptoms start and thus reversal of ongoing JC infection is crucial. Although the pharmacokinetic half-life in patients with MS is ~11±4 days, NTZ is detectable up to 200 days in the circulation after cessation of therapy. It also has been shown that mean α4-integrin saturation levels remain >70% at 4 weeks after infusion. One study showed that serum NTZ levels 1-week post TPE were reduced by an average of 92% from baseline with 75±28% reduction 4 weeks after NTZ infusion when comparing the same patients with and without TPE (Khatri, 2009). Additionally, desaturation of the α4-integrin receptor to <50% was achieved when NTZ concentration was <1 μg/mL (therapeutic level). Thus, TPE accelerates removal of NTZ, 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. However, accumulating retrospective analyses didn't find an association of apheresis and improved outcome. In a study of 219 patients with NTZ-PML, TPE was not associated with decreased mortality or residual disability (Landi, 2017). In a study of 42 patients, the duration of IRIS was longer in patients treated with TPE (Scarpazza, 2017). In a systematic review and meta-analysis including 194 patients from 62 articles there was no significant difference in the outcomes as assessed by EDSS scores between treatments given for PML, such as TPE or IA alone or in combination with IV steroids, or a combination with either anti-malarial, antivirals, or 5 HT2A receptor antagonist (Sriwastava, 2021).

Nonetheless, these retrospective studies had major limitations including relatively small numbers of patients and potential differences in baseline characteristics between the groups who received TPE and the groups who did not. Patients with the most severe presentation and subsequently worst prognosis were treated with TPE or IA putatively creating a negative bias. Thus, the benefits of immune reconstitution in patients with severe NTZ-PML may outweigh the risk of IRIS and although the role of TPE is not yet optimized in this condition. The benefits of TPE are conjectural, and have not been proven rigorously, but this modality can be considered in select patients. TPE has been also used for PML associated with fongolimod cessation.

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Technical notes

The use of IA was reported with comparable efficacy of NTZ elimination at the level of single cases. However, the risk of PML-IRIS must be regarded as essentially identical.

Volume treated: 1 to 1.5 TPV **Frequency:** Every other day

Replacement fluid: Albumin

Duration and discontinuation/number of procedures

Five TPE procedures (most commonly used in reported cases) is needed for >95% of patients to lower NTZ levels <1 μg/mL, which may be used as a post-TPE target (Khatri, 2009).

Keywords: natalizumab, progressive multifocal leukoencephalopathy, multiple sclerosis, immune reconstitution inflammatory syndrome, plasma exchange

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PRURITUS DUE TO HEPATOBILIARY DISEASES

Incidence: rare

Indication	Procedure		Category	Grade
Treatment resistant	TPE		III	1C
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	4 (14)	12 (14)

Description

Chronic pruritus can present in patients with a variety of hepatobiliary disorders including primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), 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% to 80% of patients with PBC and PSC may experience pruritus, while pruritus is less frequently seen in patients with obstructive cholestasis.

Pruritus may range from mild and tolerable to difficult and intolerable, limiting daily life activities, causing severe sleep deprivation, depression, and even suicidal ideation. Pruritus tends to intensify during the evening. Pruritus of the limbs and, in particular, palms and soles, tends to be more severe, but it can be generalized. However, no primary causative skin lesions are identified. Pruritis is affected by hormones and 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 causative 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 with both the severity of pruritus and the treatment efficacy.

Bile cast nephropathy caused by hyperbilirubinemia leading to acute kidney injury can also manifest in pruritis. There are multiple mechanisms for this effect, including direct toxicity of bilirubin on renal tubular cells. There have been a few CRs of treating bile cast nephropathy due to hyperbilirubinemia with a combination of TPE and dialysis.

Current management/treatment

Pharmacologic therapy includes: (1) first-line: anion exchange resin cholestyramine to remove the pruritogen(s) from the enterohepatic circulation in mild pruritus, (2) second-line: rifampicin to modulate central itch and/or pain signaling, (3) third-line: naltrexone (μ-opioid antagonist, to modulate central itch and/or pain signaling), and (4) fourth-line: sertraline (to modulate central itch and/or pain signaling). For patients unresponsive to medications, other measures may be used, such as: (1) nasobiliary and transcutaneous drainage or external biliary diversion to remove the pruritogen(s) from the enterohepatic circulation, (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

It has been demonstrated that TPE removes potential pruritogen(s) from the systemic circulation. Patients may experience decreased pruritus after the second TPE. For some patients, the effect may last many months, while for others, the effect may be short-lived and chronic maintenance TPE is needed.

Technical notes

Volume treated: 1 to 1.5 TPV

Frequency: 3 (weekly or biweekly) procedures initially, then 2 to 4 times per month for maintenance

Replacement fluid: Albumin

Duration and discontinuation/number of procedures

Some may require long term TPE; treatment is individualized based on patient symptoms.

Keywords: pruritus, plasma exchange, primary biliary cirrhosis, primary sclerosing cholangitis

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PSORIASIS

Incidence: ~80/100,000/year

Indication	Procedure		Category	Grade
Disseminated pustular	ECP		III	2B
	Adsorptive cytapheresis		III	2C
	TPE		IV	2C
# reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
ECP	0	0	2 (12)	1 (1)
Adsorptive cytapheresis	0	1 (44)	7 (65)	14 (18)
TPE	0	1 (6)	3 (23)	0

Description

Psoriasis is a common chronic immune-mediated, skin disorder with high genetic predisposition affecting 3% of adults and <1% of children in the United States. Plaques and papules are the result of hyperproliferation and abnormal differentiation of epidermis which leads to its thickening (acanthosis). Inflammatory infiltrate consisting of dendritic cells, macrophages, neutrophils and T cells in the dermis with some T cells in the epidermis, contribute to overall thickness of lesions. The disease process involves upregulation of Th1 and Th17 pathways with T cell transport from the dermis into epidermis as key event. Recirculation of T cells in the skin leads to keratinocyte proliferation. Imbalance is further affected by a decrease in activity but not number of T regs and decreased levels of IL-10. Complex feedback loops between the innate and adaptive immune system mediated by cytokines plays an instrumental role in the development of the pathological changes seen in psoriasis. Psoriatic T cells predominantly secrete interferon-γ and interleukin-17 while activated dendritic cells produce TNF-α and interleukin-23 (Armstrong, 2020).

Clinical types of psoriasis are plaque (psoriasis vulgaris), generalized pustular psoriasis, and psoriatric arthritis. Except for widespread pustular psoriasis, the disease rarely causes death. 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). Generalized pustular psoriasis is often present in patients with existing or previous psoriasis vulgaris but can also develop in people without a history of psoriasis. In these patients the cause is often identified as a deficiency of interleukin-36 receptor antagonist (DITRA), due to mutation of *IL36RN*.

Psoriatic arthritis, an inflammatory arthropathy, can occur in 10% to 30% of patients with psoriasis. Arthritis develops before psoriasis in up to 15% of those with psoriatic arthritis. Many genetic associations have been identified with psoriatic arthritis including HLA-B27.

Current management/treatment

Topical and systemic therapies are available. Therapy is generally dictated by disease severity, comorbidities, patient's preferences and adherence to treatment. Moderate to severe psoriasis is defined as 5% to 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). In the past decade several biologics have been approved and are recommended as second line treatment for psoriasis. TNF-alpha inhibitors (etanercept, infliximab, and adalimumab) and ustekinumab, a human monoclonal antibody against IL-12 and IL-23, are approved for treatment of moderate-severe psoriasis. Secukinumab, ixekizumab, brodalumab, and bimekizumab have been approved as the monoclonal antibody blocking IL-17, a key effector cytokine produced by TH17 and other cells. Clinical response is often evaluated using Psoriasis Area and Severity Index (PASI score; 0 to 72) which evaluates 3 features of psoriatic plaque (redness, scaling and thickness) and extent of involvement of each body area. The complexity and variety of treatments over time is demonstrated in a registry study in pustular psoriasis (Ohata, 2022).

Rationale for therapeutic apheresis

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. Granulocyte and monocyte adsorption apheresis (GMA) removes activated granulocytes and monocytes using a column packed with cellulose acetate beads. The selective removal of leukocytes through the column provides for a reasonable pathophysiological justification especially in context of disseminated pustular psoriasis or mutation of *IL36RN* (Mizutani, 2020; Fujii, 2019). In one study, 15 patients received 5 treatments (1/week) in addition to standard therapy. There was 86% response rate, though the contribution of apheresis is difficult to discern as other therapies were used concurrently (Ikeda, 2013). Several smaller studies confirmed improvement in clinical symptoms. In a study of 20 patients with refractory psoriatic arthritis, 65% of patients demonstrated a 20% improvement in joint symptoms and signs following 5 to 10 GMA sessions. This response was maintained in at least 28% of patients for over 20 weeks (Kanekura, 2017). The use of lymphocytapheresis using MNC has been described in several earlier small studies. Lymphocytapheresis was performed by an automated centrifuge-based continuous-flow blood cell separator. The rationale for its use is similar to described above. The reported response rate was similar to that shown with adsorptive granulocyte-monocyte columns. However, apheresis

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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. Several studies have shown a variable response (Adamski, 2015). Apheresis procedures can be used when the use of immunosuppressive drugs and/or biologics is contraindicated due to patient comorbidities (Fujii, 2019; Trivedi, 2018).

Technical notes

Granulocyte-monocyte adsorptive columns are not available in the United States.

Volume treated: Adsorption: 1,500 to 2,000 mL; ECP: varies

Frequency: Adsorption: 1/week; ECP: one cycle/week for 4 months and then taper

Replacement fluid: NA

Duration and discontinuation/number of procedures

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

Keywords: psoriasis, cascade filtration, lymphocytapheresis, extracorpeal photopheresis, plasma exchange, adsorptive cytapheresis

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RED BLOOD CELL ALLOIMMUNIZATION, PREGNANCY COMPLICATIONS

Incidence: hemolytic disease of the fetus and newborn: 1,700 cases/100,000 newborns (United States)

Indication	Procedure		Category	Grade
Hemolytic disease of the fetus and newborn	TPE		III	2C
RhD alloimmunization prophylaxis after transfusion	RBC exchange		IV	2C
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Hemolytic disease of the fetus and newborn	0	0	>10 (>200)	NA
RhD alloimmunization prophylaxis after transfusion	0	0	0	6 (8)

Description

RBC alloimmunization is a complication of RBC transfusion but can also occur in the setting of pregnancy and/or transplantation. Patients with RBC alloantibodies are at risk for hemolytic transfusion reactions and it can be difficult to find compatible RBC units. For people of childbearing potential (PCP), alloimmunization can also cause hemolytic disease of the fetus and newborn (HDFN). In HDFN, maternal IgG crosses the placenta causing hemolysis of fetal RBCs, leading to fetal anemia and when severe, hydrops fetalis and death. HDFN severity increases with subsequent pregnancies. Traditionally severe HDFN is secondary to anti-D, but it can be caused by other alloantibodies (e.g., anti-K, -C/c, -E, -PP1Pk). Prophylactic Rh immunoglobulin (RhIg) during pregnancy and post-partum has significantly reduced HDFN secondary to anti-D.

Generally patients are transfused ABO and RhD compatible RBCs to prevent RhD alloimmunization. In the setting of life threatening bleeding or low inventory, protocols are in place to provide RBCs rapidly without the patient's blood type. Due to the limited availability of RhD negative (RhD-) RBC units (<15% of blood donors are RhD-) use in emergencies is often restricted to PCP with others receiving Group O, RhD positive (RhD+) RBCs. To mitigate the risk of anti-D formation in PCP who received RhD+ RBCs, several strategies have been attempted, including RBC exchange and/or RhIg.

Current management/treatment

The following describes management of a pregnant patient with a newly identified clinically significant RBC alloantibody who is at risk for HDFN: (1) history is obtained to identify exposure source (e.g., previous pregnancy, transfusion, transplant, IV drug use, etc.), (2) presumed father's RBCs are typed to assess for risk of inheritance. If the presumed father does not express the antigen, the fetus is deemed low risk. If the presumed father's RBCs express the antigen, further testing determines whether the father carries 1 or 2 gene copies. (3) Sensitized pregnancies are monitored with RBC antibody titer and by middle cerebral artery (MCA) Doppler ultrasound (US) with velocimetry to detect fetal anemia. Critical titer thresholds are typically 8 to 32 though titer does not always correlate with risk/severity of HDFN (e.g., anti-Kell). (4) If the titer is above a critical threshold or increased by 2 dilutions, serial US should be performed. Institutions use US with velocimetry at 18 weeks gestational age (GA) to determine treatment rather than titer. Moderate-severe anemia is predicted when MCA measurement is >1.5 multiples of the median (MoM). (5) After this, cordocentesis assesses fetal hematocrit (HCT); if HCT <30%, intrauterine transfusion (IUT) is indicated. IUT cannot be technically or safely performed until ~20 weeks GA. (6) Amniocentesis for fetal lung maturity assessment determines whether the fetus can be safely delivered. (7) HDFN can cause neonatal hyperbilirubinemia, which can result in kernicterus so the neonate must be monitored.

RBC exchange following exposure to RhD+ RBCs reduces the volume of RhD+ RBCs allowing for safe RhIg administration. Studies have found the rate of RhD alloimmunization in patients who are RhD- following RhD+ RBC transfusions is approximately 20% (Yazer, 2019). This rate is lower than the historical rate of 80%, which was determined in healthy prisoners. Proceeding with therapy to prevent RhD alloimmunization should be based on the risks of therapies balanced with the risk of RhD alloimmunization and potential for HDFN.

Rationale for therapeutic apheresis

In the setting of HDFN, TPE may decrease the maternal antibody titer and amount of antibody transferred to the fetus, decreasing RBC destruction improving HDFN. The current mainstay of treatment is IUT, but if there is a high risk of fetal demise or signs of hydrops at <20 weeks GA, especially in a mother with a previously affected pregnancy, then TPE and/or IVIG may be indicated. Survival in severe cases with the use of TPE and/or IVIG prior to IUT is ~75%. Most patients also received IVIG and IUT. One CS highlighted the use of IA for severe Rh HDFN unresponsive to TPE and IVIG (Colpo, 2017). Another reported on the rebound effect TPE may have in alloantibody production (Barclay, 1980). TPE has not been shown to prevent future fetal anemia and subsequent IUT.

The goal of RBC exchange post-transfusion is to reduce circulating RhD+ RBCs to a level at which RhIg can be safely administered to prevent alloimmunization and potentially HDFN. However, HDFN can be safely managed in the majority of cases. In one retrospective study, outcomes of neonates born to alloimmunized mothers were favorable, with a low incidence of HFDN (0.6/1000; Lieberman, 2020). Another study reported a 96% overall survival rate of fetuses that received at least one IUT due to alloimmunzation (Zweirs, 2018). This data has led some authors to question whether RhD− RBCs must be transfused to RhD− PCP in bleeding emergencies (Yazer, 2019). Though most cases of HDFN are caused by RhD antibodies, other Rh and Kell antibodies are associated with a high risk of severe HFDN (Liu, 2021). Thus, the risk of sensitizing a PCP to additional antigens through RCE to avoid alloimmunization to RhD is not insignificant and likely outweighs the potential benefit.

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Technical notes

Reports varied on maternal TPV to exchange for HDFN, 1 was average. TPE is performed prior to intrauterine transfusion availability, which is not typically performed until GA is ≥20 weeks. For RBC exchange, target fraction of RBCs remaining should be tailored to the volume of RhD+ RBCs received to achieve a volume that can be safely treated with RhIg. Authors varied on how much to exchange, 1 RCV was typical. If exchange is being performed to reduce Rh+ cells, the RBCs chosen should be phenotypically matched for C, E, Kell, Duffy, Kidd, and S to avoid alloimmunization to these antigens as well, since they can also cause HDFN.

Volume treated: RBC exchange: 1 to 2 RCV; TPE: 1 to 1.5 TPV **Frequency:** 1 to 3/week

Replacement fluid: RBC exchange: RhD- antigen matched RBC units; TPE: albumin

Duration and discontinuation/number of procedures

TPE should be considered early in pregnancy (7-20 weeks) and continued until IUT can safely be administered (~20 weeks GA). Close monitoring of the fetus for signs of hydrops aids in guiding treatment.

Keywords: hemolytic disease of the fetus and newborn, red cell alloimmunization, IUT, hydrops, plasma exchange, IVIG, Rh immunoglobulin, red cell exchange, RhD, Rh+

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SEPSIS WITH MULTIORGAN FAILURE

Incidence: severe sepsis in adults 300/100,000/year (United States); 8% prevalence in pediatric intensive care

Indication	Procedure	Category		Grade	
	TPE	III		2A	
# reported patients: >300	**Procedure**	**RCT**	**CT**	**CS**	**CR**
Sepsis*	TPE	5 (234)	7 (295)	NA	NA
Sepsis, COVID-19 related	TPE	1 (87)	6 (359)	NA	NA

*excluding sepsis due to COVID-19

Description

Sepsis is a systemic inflammatory response to infection in which multiple toxic mediators lead to tissue injury, multiple organ dysfunction (MODS), disseminated intravascular coagulopathy (DIC), and immune dysregulation. In studies from seven high-income countries during 1979 to 2015, the incidence of severe sepsis was 270/100,000/year with 26% mortality. Risk factors for sepsis 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 including tumor necrosis factor (TNF), interleukins (IL), leukotrienes, prostaglandins, endotoxin, and transforming growth factor-β (TGF-β) are part of the inflammatory state in sepsis. Coagulopathy, microvascular occlusion, and tissue ischemia appear to be connected to derangements in the balance of ADAMTS13 (a disintegrin and metalloprotease with thrombospondin motifs-13) enzyme activity and von Willebrand factor multimers.

Current management/treatment

Management includes antimicrobial agents, control of the source of the infection, and hemodynamic support including volume, vasopressors, and mechanical ventilation. Additional treatments including corticosteroids, IVIG, anticoagulation, and immunomodulatory agents have been utilized; however, there is not broad acceptance of any one of these therapies.

Rationale for therapeutic apheresis

TPE is postulated to improve organ function by removing inflammatory and antifibrinolytic mediators, and replenishing anticoagulant proteins and ADAMTS13 with plasma replacement, thereby mitigating and reversing complex, dysregulated pathways of sepsis and restoring hemostasis. Observational studies of TPE noted survival rates of 60% to 87% compared to historical controls (survival rates ~20%-40%). Several CS suggest early treatment is beneficial compared to delayed initiation of therapy, and that TPE may lead to hemodynamic stabilization. In a retrospective cohort study of 42 pediatric patients diagnosed with thrombocytopenia-associated multiple organ failure (TAMOF), those who received TPE treatment had improved 28-day mortality ($P = .006$), even after controlling for illness severity ($P = .048$; Sevketoglu, 2014). In another cohort study examining pediatric sepsis, mortality was higher in the TPE group (32%) versus the control group (14%), despite controlling for patient comorbidities ($P<.001$), but may have been confounded by greater use of TPE in sicker patients (Lima, 2018). An observational cohort study of 81 children found TPE was associated with reduced 28-day mortality by multivariate analysis ($P = .02$) with improved Pediatric Logistic Organ Dysfunction (PELOD) scores (Fortenberry, 2019).

Unlike the observational studies suggestion of efficacy, results from RCTs have been conflicting. Five RCTs of 10 to 106 patients using TPE have been published. The largest of these RCTs in patients with severe sepsis utilized 1-2 daily TPE treatments resulting in 28-day mortality rate of 33% in the TPE group and 54% in the control group ($P < .05$), which became non-significant ($P = .07$) when controlled for confounding factors (Busund, 2002). Another RCT used continuous plasma filtration in 22 adults and 8 children (Reeves, 1999). Although there was no difference in 14-day mortality, reduction of acute phase reactants such as C3, C-reactive protein, and haptoglobin was achieved. In a RCT of 48 adults and children, which compared plasma filtration to standard therapy, there was no significant difference in 28-day mortality (Long, 2013). One RCT in 10 children with severe sepsis and TAMOF randomized standard treatment with or without TPE (Nguyen, 2008). A significant decrease in multiple organ severity scores ($P < .001$) and improved 28-day survival ($P < .05$) was seen in the TPE group, who received a median of 12 TPE treatments. While 2 of 4 aforementioned RCTs (Long, 2013; Nguyen, 2008) did not meet projected enrollment (making interpretation difficult) and were deemed to be at "unclear to high risk" of bias, a meta-analysis found TPE was not associated with a significant reduction in all-cause mortality (Rimmer, 2014). In subgroup analysis, TPE was associated with reduced mortality in adults ($P < .05$), but not in children. A RCT of 40 patients in septic shock found a single TPE treatment resulted in greater reduction in norepinephrine requirements, serum lactate levels, inflammatory biomarkers (e.g., pro-calcitonin), and repletion of protective factors (e.g., ADAMTS13) leading to preserved hemodynamic stabilization in the TPE group (all indices $P < .05$) despite only seeing a trend toward reduced mortality ($P = .095$; Stahl, 2022). In an 80-patient retrospective observational study, 37 patients with septic shock received 1 to 5 TPE sessions resulting in decreased 28-day mortality (TPE 40% vs. control 65%, $P = 0043$; Keith, 2020).

In a RCT of 87 patients with severe COVID-19 disease, 43 patients in the TPE group underwent 5 daily TPE treatments and had fewer days of mechanical ventilation, shorter ICU stays, lower Sequential Organ Failure Assessment (SOFA) scores and inflammatory lab results (such as lactate dehydrogenase, ferritin, IL-6), and higher PaO_2/FiO_2 ratios and ADAMTS13 activity than the control group ($P<.05$; Faqihi, 2021). In 6 CTs studying the effects of 1 to 5+ (median of 4) daily TPE treatments in severe COVID-19 infection, 83% (5/6) demonstrated significant decreases in inflammatory markers, and 67% (4/6) showed improved 28-day mortality in the TPE group ($P<.05$).

In evaluating 487 patients with sepsis/septic shock/MODS, 5 RCTs and 4 CTs studied the effectiveness of hemoadsorption (HA) columns/filters to decrease inflammatory biomarkers and all-cause mortality. Three studies involved patients with severe COVID-19 disease, ARDS, and sepsis. Six trials utilized HA columns in tandem with continuous renal replacement therapy (CRRT) and three in tandem with extracorporeal membrane oxygenation (ECMO). In 56% (5/9) of these studies, no significant changes in inflammatory mediators were measured over 7 to 10 days; in 67% (6/9) of these trials,

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there were no significant improvements in 30 to 60 day mortality (Supady, 2021; Stockmann, 2022). Meta-analyses of matched cohort studies and RCTs with polymyxin B hemoperfusion found decreases in mortality ($P = .007$; Chang, 2017), but no significant impact on 28-day mortality when only RCTs were analyzed ($P = .112$; Kuriyama, 2018).

Technical notes

Centrifugal-based and filtration-based instruments are used. Blood purification techniques (other than TPE) have been used, including hemoperfusion, hemofiltration, and hemodiafiltration. Apheresis procedures in tandem with ECMO have been utilized.

Volume treated: 1 to 1.5 TPV **Frequency:** Daily

Replacement fluid: Plasma

Duration and discontinuation/number of procedures

TPE treatments ranged from 1-2 to 14 days or resolution of symptoms. HA column therapy: median 3 days (range 2-7 days).

Keywords: plasma exchange, hemoadsorption, sepsis, septic shock, COVID-19, SARS-CoV-2

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SICKLE CELL DISEASE, ACUTE

Incidence: 273/100,000/year (1/375 for Hb SS, 1/835 for Hb SC, 1/1667 for Hb S/ß-thalassemia)

Indication	Procedure		Category	Grade
Acute stroke	RBC exchange		I	1C
Acute chest syndrome, severe	RBC exchange		II	1C
Other complications*	RBC exchange and/or TPE**		III	2C
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Acute stroke	0	0	10 (241)	NA
Acute chest syndrome	0	2 (121)	>10 (>200)	NA
Other complications*	0	0	>10 (>200)	NA

*Includes priapism, multiorgan failure, splenic/hepatic sequestration, intrahepatic cholestasis, and bone marrow necrosis/fat embolism syndrome; **includes patients who received TPE following RBC exchange or TPE alone.

Description

Sickle cell disease (SCD) affects ~100,000 people in the United States. It is caused by abnormal sickle hemoglobin (HbS), formed by the substitution of valine for glutamic acid in the gene that encodes the hemoglobin beta-globin chain. HbS polymerizes upon deoxygenation and RBCs become rigid and deformed, resulting in chronic hemolytic anemia and a shortened RBC lifespan (~10-20 days). Sickled RBCs increase blood viscosity and occlude the microvasculature, causing tissue hypoxia and infarction. The overall SCD mortality rate is ~3% (0.5 deaths/100-person years) with historic data indicating peak mortality at 1 to 3 years (Leikin, 1989). The average life expectancy is ~54 years. The leading causes of death are sepsis, acute chest syndrome (ACS), stroke, acute multiorgan failure (MOF), and pulmonary hypertension. Life expectancy has increased with the use of penicillin prophylaxis.

Acute SCD manifestations are vaso-occlusive crises (VOCs), including stroke, ACS, priapism, splenic sequestration, intrahepatic cholestasis, kidney dysfunction, and bone marrow necrosis/fat embolism syndrome. Ischemic stroke can be overt, occurring in up to 10% of patients, or silent, occurring in 20% to 35%, with a recurrence rate of 46% to 90%. The highest stroke risk occurs in patients with the genotypes HbSS and HbSß0. ACS is defined by sudden decreased oxygen saturation despite oxygen therapy in the setting of new chest x-ray infiltrate and is often accompanied by fever, tachypnea, cough, and chest pain. ACS incidence is highest in young children (2-5 years). ACS is likely due to RBC sickling in the pulmonary vascular space and can be idiopathic or associated with infection, pulmonary infarction, or fat embolism. Priapism (painful sustained erection >4 hours) can affect up to 35% of at risk patients with SCD. Other acute manifestations of SCD that occur rarely are MOF, splenic/hepatic sequestration, intrahepatic cholestasis, and bone marrow necrosis/fat embolism syndrome.

Current management/treatment

Primary and secondary prevention with chronic transfusion therapy has resulted in significant stroke rate reduction (see Sickle cell disease, non-acute); nevertheless, residual risk exists. When patients present with acute focal neurologic deficits or mental status changes, imaging studies should be urgently performed to evaluate for stroke. The absence of an MRI abnormality does not definitively exclude the stroke diagnosis. Therefore, high clinical suspicion, even when not confirmed by imaging studies, should prompt immediate transfusion therapy. Due to higher rates of recurrence with simple transfusion alone (Hulbert, 2006), emergent RBC exchange is recommended. By removing HbS, RBC exchange reduces blood viscosity and improves oxygen carrying capacity. ACS treatment includes supportive care with antibiotics (cephalosporin, macrolide), oxygen supplementation (target ≥95% SaO2), and close monitoring. If Hb level is ≥1 g/dL below baseline and <9 g/dL, RBCs should be transfused. For severe ACS, as demonstrated by rapid clinical progression of hypoxia (SaO2 ≤90%), emergent RBC exchange is recommended. Priapism should be treated with vigorous hydration and analgesia with urology consultation 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 to 48 hours. MOF presents as unexpected life-threatening VOC involving three or more organs such as the lung, liver, and kidney. Management includes expedient evaluation and support of vital functions (ventilation, hemodialysis), and RBC transfusion or exchange. A small CS reviewed 4 patients with SCD and MOF initially treated with RBC exchange. After no improvement, TPE was performed with clinical improvement observed in 3 of 4 patients (Louie, 2018). Splenic/hepatic sequestration and intrahepatic cholestasis management includes hydration and surgical consult, and simple transfusion or RBC exchange. In these cases, RBC transfusion or RBC exchange resulted in a better outcome in 11 patients (0% compared to 20% mortality with historical controls).

Rationale for therapeutic apheresis

In acute manifestations of SCD, the decision to use RBC transfusion, manual or automated RBC exchange is guided by weighing the risk of the apheresis procedure against the patient's condition, and ability to quickly obtain apheresis services, intravenous access, and blood products. RBC exchange offers more efficient and rapid removal of sickled RBCs and keeps the patient isovolemic and iron stores net even. For patients with their first stroke, RBC exchange (manual or automated) appears to lower the stroke recurrence rate compared with RBC transfusion (21% [8/38] vs. 57% [8/14], respectively; Hulbert, 2006). A retrospective review of 81 pediatric patients with ACS found that RBC exchange in the children with worse pulmonary function equalized them to achieve a similar hospital course to those children with less severe pulmonary function at the start of the admission (Saylors, 2013). A small study of 5 patients with SCD showed that the median time to oxygen saturation recovery on room air was 24 hours after RBC exchange (Aneke, 2016). Side effects of RBC exchange in acute SCD manifestations include central venous catheter thrombosis and hemorrhage, which can be mitigated with placement in internal jugular site compared to the femoral vein location. In patients with acute SCD complications unresponsive to

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RBC exchange, a minority of studies have described use of TPE for MOF, ACS, intrahepatic cholestasis, and bone marrow necrosis/fat embolism syndrome. Some studies have used TPE without RBC exchange in patients with or at risk for hyperhemolytic crisis. The rationale for TPE is removal of inflammatory cytokines, chemokines, and acute phase proteins in plasma that may be involved in VOC pathophysiology.

Technical notes

Apheresis practitioners should decide the target HCT and either the desired FCR (fraction of patient's RBCs remaining at end of procedure) OR the target volume to be exchanged. In general, it is best to determine the FCR required to achieve target HbS of <30% (or HbS + HbC of 30%, etc.) at the end of the procedure. The end HCT should be 30 ± 3% (≤ 33% to avoid hyperviscosity), as clinically indicated (Biller, 2018). Once these parameters are decided, the apheresis machine will determine the volume necessary to exchange. Patients with unstable blood pressure may not tolerate RBC exchange.

Volume treated: Volume necessary to achieve target HbS level

Replacement fluid: RBC units, HbS negative, leukocyte reduced, antigen-matched (e.g., C/c, E/e, K); for TPE, the predominant replacement is plasma

Frequency: Once

Duration and discontinuation/number of procedures

Typically one RBC exchange procedure achieves the desired HbS level.

Keywords: sickle cell disease, red blood cell exchange, therapeutic plasma exchange, transfusion, stroke, acute chest syndrome, priapism, multiorgan failure, bone marrow necrosis, fat embolism syndrome

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SICKLE CELL DISEASE, NON-ACUTE

Incidence: 273/100,000 (1/375 for Hb SS; 1/835 for Hb SC; 1/1667 for Hb S/ß-thalassemia)

Indication	Procedure		Category	Grade
Stroke prophylaxis	RBC exchange		I	1A
Pregnancy/Recurrent vaso-occlusive crises	RBC exchange		II	2B
Pre-operative management	RBC exchange		III	2A
# reported patients: >300*	**RCT**	**CT**	**CS**	**CR**
Stroke prophylaxis	2 (326)	2 (49)	NA	NA
Pregnancy	0	5 (170)	7 (113)	NA
Recurrent vaso-occlusive crises	0	2 (32)	12 (90)	NA
Pre-operative management	3 (1035)	4 (184)	NA	NA

*Includes RBC transfusion, manual RBC exchange or automated RBC exchange.

Description

Sickle cell disease (SCD) affects ~100,000 people in the United States. It is caused by abnormal sickle hemoglobin (HbS), formed by the substitution of valine for glutamic acid in the gene that encodes the hemoglobin beta-globin chain. HbS polymerizes upon deoxygenation and RBCs become rigid and deformed, resulting in chronic hemolytic anemia and a shortened RBC lifespan (~10-20 days). Sickled RBCs increase blood viscosity and occlude the microvasculature, causing tissue hypoxia and infarction. The overall SCD mortality rate is ~3% (0.5 deaths/100-person years) with historic data indicating peak mortality at 1 to 3 years (Leiken, 1989). The average life expectancy is ≥50 years. Leading causes of death include sepsis, acute chest syndrome (ACS), stroke, acute multiorgan failure (MOF), and pulmonary hypertension (PH). Chronic complications of SCD can begin at an early age and include recurrent vaso-occlusive crises (VOC), end organ damage, avascular necrosis of bones, cholelithiasis, and PH. Complications from chronic therapy, such as iron overload and alloimmunization, are also common, particularly in patients receiving simple blood transfusions. Chronic VOC (>3 months) occurs in up to 55% of patients with SCD with PH occurring in 6% to 10%. If chelation therapy is not used, many chronically transfused patients with SCD may become iron overloaded.

Current management/treatment

RBC transfusion is a mainstay of long-term SCD therapy that is supported by multiple RCTs. In the STOP trial for primary stroke prevention, children with elevated blood flow velocity (a predictor of stroke risk) were randomized to standard supportive care without transfusion (control) versus chronic monthly transfusion (Adams, 1998). The trial was terminated prematurely due to the marked (90%) stroke risk reduction by chronic transfusion. Another trial found that chronic RBC transfusion was also efficacious in secondary stroke prevention/progression in children with evidence of silent cerebral infarct on imaging (DeBaun, 2014). Transfusion withdrawal was associated with increased risk of recurrent stroke. For chronic transfusion therapy in a clinically stable patient, targeting a pre-transfusion HbS threshold of 50% may be as effective as 30%. Several studies have shown decreased frequency of recurrent VOC with monthly manual RBC exchange. Surgery is associated with high rates of SCD related complications. The TAPS RCT demonstrated that pre-op transfusion was associated with decreased perioperative complications (39% non-transfused vs. 15% transfused; Howard, 2013). Pre-op transfusion should target a Hgb of 10 g/dL. For patients with high baseline Hgb 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).

SCD disease modifying therapies include hydroxyurea (HU), crizanlizumab, and L-glutamine. HU, which increases HbF%, reduces VOC episode frequency, ACS, and other complications, and is associated with reduced transfusion and hospital admissions. In pediatric patients with prior stroke, the SWiTCH RCT showed that HU therapy plus phlebotomy did not replace chronic RBC therapy for secondary stroke prevention (Ware, 2011). However, the TWiTCH trial demonstrated that, in patients with abnormal TCD velocities, HU is an acceptable substitute for chronic transfusions to maintain TCD velocities and prevent primary stroke (Ware, 2016). Crizanlizumab is a monoclonal antibody against P-selectin that reduces VOC. In the SUSTAIN RCT, high dose crizanlizumab significantly decreased VOC compared to placebo (36 vs. 17 %; Ataga, 2017). L-glutamine is an amino acid that may impact the oxidative state of RBCs. Compared to placebo, L-glutamine was shown in an RCT to decrease acute pain events (4 vs. 3), hospitalizations (3 vs. 2) days in the hospital (11 vs. 7) and ACS (23 vs. 9%; Niihara, 2018). Another SCD therapy is voxelotor, an HbS polymerization inhibitor that does not decrease VOC but may improve anemia. Hematopoietic stem cell transplantation is a potentially curative therapy, however, indications, appropriate donor sources and preparative regimens are being defined to optimize outcomes.

Rationale for therapeutic apheresis

When compared to simple transfusion or manual RBC exchange, automated RBC exchange removes/replaces HbS more efficiently. RBC exchange may also have beneficial effects on blood viscosity, vessel relaxation time, and reduction of adhesion molecule levels like sVCAM-1. One report suggests that RBC exchange reduces cerebral blood flow and oxygen extraction fraction, thereby relieving cerebral metabolic stress and mitigating infract risk (Guilliams, 2018). RBC exchange, particularly in conjunction with isovolumic hemodilution (RBC depletion with 0.9% NaCl replacement followed by standard RBC exchange), can remove or keep iron stores steady in patients with iron overload. The 2015 ASFA consensus conference on the management of patients with sickle cell disease supports RBC exchange with and without isovolemic hemodilution (IHD) to reduce or prevent iron overload (Sarode, 2015). In 36 pediatric patients compared to matched controls, long-term RBC exchange for a mean of 5 years was associated with improved growth velocity without increased risk of iron overload (Bavle, 2014). Chronic RBC exchange has also been described in pregnancy. In pregnancy, RBC transfusion and RBC exchange have been associated with lower risk of maternal and neonatal mortality, intrauterine growth restriction, and other fetal complications, and decreased rate of maternal complications. RBC exchange has been used to manage PH, which improves SaO2 and ability to execute activities of daily life. RBC exchange is increasingly used in the management of priapism, when other therapies have been unsuccessful.

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Technical notes

Chronic vascular access remains a concern in RBC exchange (Otrock, 2018). Apheresis compatible ports have been used successfully in adults though with longer procedures and more complications. A CS demonstrated feasibility with arterior-venous fistulas for long term access, but the risk/benefits need to be discussed (Delville, 2016). Apheresis equipment software calculates the replacement RBC volume to achieve target HbS (fraction of RBCs remaining at procedure end) and HCT. General guidelines are: (1) end HCT at 30 ± 3% (<33%-36% to avoid hyperviscosity) and (2) HbS (or HbS +HbC) of <30%, etc. However, providers tend to target a lower HbS goal of <15% so that the next pre-procedure HbS is <30%. IHD is a procedure modification used in select patients whose hemodynamics and pre-procedure hematocrit indicate that they are able to tolerate the procedure. IHD reduces replacement RBC volume and donor exposure, helping decrease transfusion related iron overload. At the end of the IHD phase, the target threshold is up to a maximum HCT of 6% to 8% below the pre-procedure HCT, as tolerated.

Volume treated: Volume necessary to achieve target HbS level

Replacement fluid: RBC units, HbS negative, leukocyte reduced, antigen-matched (e.g., 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.

Keywords: sickle cell disease, red blood cell exchange, transfusion, stroke, iron overload, pregnancy

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STEROID-RESPONSIVE ENCEPHALOPATHY ASSOCIATED WITH AUTOIMMUNE THYROIDITIS

Incidence: rare				
Procedure	**Category**		**Grade**	
TPE	II		2C	
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	0	25 (27)

Description

Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT), formerly Hashimoto's encephalopathy, 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, though with typically two distinct presentations. For most patients (∼75%), it may present as an indolent form associated with depression, confusion, cognitive decline, myoclonus, tremors, and fluctuations in level of consciousness. This form is commonly associated with a more progressive disease. The less common type is an acute onset of episodes of stroke-like symptoms, seizure, and psychosis, and this presentation is usually associated with a relapsing-remitting course. The mean age of onset is about 40 to 50 years. Imaging, EEG, and cerebrospinal fluid 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 (anti-TPO), followed by antithyroglobulin antibodies; however, these are not specific for this diagnosis. Furthermore, the titer of antithyroid antibodies does not correlate well with clinical symptoms or severity of the disease. There is no evidence that anti-thyroid antibodies are harmful to neurons. 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. Other biomarkers include anti-alpha-enolase antibody, which has been shown to increase in 68% to 83% of patients diagnosed with SREAT.

Current management/treatment

High dose corticosteroids are the first line therapy, with 88% of cases achieving response. Common steroid regimens include IV methylprednisolone (500-1000 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 who relapse, secondary therapies, such as immunosuppressive agents, have been used with variable efficacy. IVIG for steroid-unresponsive patients has shown successful clinical response in some CRs. Azathioprine or cyclophosphamide after steroid pulse has also been successful. Rituximab has been utilized to reduce the breakthrough events in patients with SREAT. Levetiracetam, an anti-epileptic medication that has anti-inflammatory effect, has been reported to be effective in 2 cases.

Rationale for therapeutic apheresis

Although the pathogenesis is unknown, an autoimmune process is believed to play a role. In the published cases to date, TPE was performed in adult and pediatric patients who failed to respond to steroids with some patients demonstrating symptomatic improvements.

Technical notes

Volume treated: 1 to 1.5 TPV

Frequency: Daily to every other day

Replacement fluid: Albumin

Duration and discontinuation/number of procedures

Published CRs used 3 to 9 procedures, mostly commonly five.

Keywords: Hashimoto encephalopathy, antithyroid antibodies, steroid-responsive encephalopathy associated with autoimmune thyroiditis, plasma exchange

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STIFF-PERSON SYNDROME

Incidence: 1/1,000,000/year

Procedure	Category		Grade	
TPE	III		2C	
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	0	0	8 (361)	NA

Description

Stiff-person syndrome (SPS) is a rare acquired autoimmune disorder of the central nervous system characterized by fluctuating, progressive, painful muscle rigidity and spasm of the trunk and limbs as well as co-contractions of agonist and antagonist muscles with continuous involuntary firing of motor units at rest. Hyperlordosis due to the episodic arching and stiffness of the lumbar spine is a diagnostic hallmark of SPS. SPS is often associated with autoimmune diseases. Concomitant type I diabetes mellitus and autoimmune thyroiditis are observed in up to 35% and 30% of cases respectively. Most cases present between ages 20 to 50 years with only 5% presenting in childhood. Autoantibodies reactive to 65 kDa glutamic acid decarboxylase (GAD65), the enzyme responsible for the synthesis of GABA in the brain and pancreatic islet cells, are present in the serum in up to 85% of patients with SPS. These antibodies block GABA synthesis. GAD65 antibodies are also present in 20% of patients with progressive encephalomyelitis with rigidity and myoclonus (PERM), a stiff-person syndrome spectrum disorder (SPSD) that is more frequently associated with anti-glycine-α1 receptor (anti-GlyR) antibodies. GAD65 antibodies may also be present in other clinical syndromes including cerebellar ataxia and limbic encephalitis. Seronegative individuals for GAD65 are more likely to have a coexisting cancer (25% vs 4%), including breast, colon, small cell lung cancer, Hodgkin's lymphoma and malignant thymoma. The paraneoplastic form of the syndrome is associated with autoantibodies to the 128 kDa synaptic protein amphiphysin.

Current management/treatment

Treatment consists of pharmacologic therapies including immune therapy (IVIG, steroids, rituximab, tacrolimus), anti-anxiety medication (diazepam, clonazepam), muscle relaxants (baclofen, tizanidine), anticonvulsants (levetiracetam, gabapentin, valproate), and pain medication. High-dose IVIG (2 gm/kg in 2-5 days) is effective in relieving symptoms of stiffness and spasticity, and in reducing the titer of anti-GAD65 antibodies. Use of subcutaneous immunoglobulin has been reported as an alternative for patients who cannot tolerate IVIG (Aljarallah, 2021). Studies have explored the use of autologous hematopoietic stem cell transplantation for SPS with mixed results (Burt, 2021; Kass-Iliyya, 2021).

Rationale for therapeutic apheresis

The association of specific autoantibodies with SPS has led CRs and CS describing responses to TPE in conjunction with other immunosuppressive therapies with positive and negative results. There are no RCT data. In reports of patients receiving TPE, >60% of patients had some improvement in symptoms. Patients with disease progression after response to an initial series of treatments may respond to additional series (Pagano, 2017). Some patients who have responded to an initial series have continued with maintenance therapy for symptom control (Albahra, 2019). Although serum and CSF GAD65 antibody titers do not appear to correlate with disease activity, one CR demonstrated the association between declining serum antibody levels, the timing of TPE and treatment response (Farooqi, 2015).

Technical notes

TPE may be considered for patients who do not respond to conventional therapy. TPE should be used as an adjunct with standard pharmacological therapy. If TPE is offered to a patient with SPS, the patient should be made aware of the paucity of clinical data to support its use and of the availability of IVIG as an alternative. If IVIG is not available or poorly tolerated, it may be reasonable to proceed with TPE. TPE can effectively deplete normal immunoglobulins when multiple plasma volumes are exchanged in a brief period.

Volume treated: 1 to 1.5 TPV **Frequency:** Every 1 to 3 days

Replacement fluid: Albumin

Duration and discontinuation/number of procedures

An initial series of 5 TPEs of 1 to 1.5 TPV is typically performed over 8 to 14 days. 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 maintenance TPE every 1 to 3 weeks for chronic treatment has also been reported.

Keywords: stiff-person syndrome, stiff-man syndrome, progressive encephalomyelitis with rigidity and myoclonus, plasma exchange, apheresis

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SUDDEN SENSORINEURAL HEARING LOSS

Incidence: 5 to 27/100,000/year

Procedure	**Category**		**Grade**	
LA/DFPP/TPE	III		2A	
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
LA*	4 (390)	0	NA	NA
DFPP	1 (240)	1 (52)	3 (43)	NA
TPE	0	0	1 (16)	1 (1)

*HELP-apheresis.

Description

Sudden hearing loss is defined as subjective hearing impairment in one or both ears that occurs over a 72-hour period. Idiopathic sudden sensorineural hearing loss (SSHL) is usually unilateral (>90%) and can range from mild to total. SSHL typically exhibits hearing loss of at least 30 decibels affecting at least 3 consecutive frequencies in the standard pure tone audiogram, usually defined in relation to the opposite ear's thresholds. Hearing loss has a wide age distribution (average 50-60 years) and may be accompanied by tinnitus (80%), aural fullness (80%) and vertigo (30%). Clinical presentation has some overlap with the diagnosis of autoimmune ear disease (AIED), for which subacute presentation is more common. SSHL is a complex disease influenced by interactions between multiple internal and external pathogenic factors, for example, noise, heredity and environment, infection, vascular impairment of inner ear blood flow in the terminal labyrinthine artery, ototoxicity, trauma, autoimmunity, neoplastic disease, endolymphatic hydrops and central nervous system disease. Hypercholesterolemia and hyperfibrinogenemia are associated with increased risk to develop SSHL; however, no thresholds have been confirmed for individual risk assessment.

Current management/treatment

SSHL has a spontaneous early recovery rate of 40% to 65%. Although there is no longer a consensus that SSHL must be considered an otological emergency, conductive hearing loss and non-idiopathic causes (e.g., acoustic neuroma, stroke, malignancy, noise, ototoxic medications) should be ruled out expeditiously. Decreasing inflammation and improving blood flow have been major considerations for historical pharmacologic therapeutic approaches (pentoxifylline, IV dextran, IV hydroxyethyl starch, IV glycerol), however, efficacy was never convincingly proven and these medications are not considered therapeutic options by current US guidelines (Chandrasekhar, 2019). Current first-line treatment options for SSHL are oral steroids, or intra-tympanic steroid injections, and as salvage therapy steroids plus hyperbaric oxygen therapy. Oral steroids are suggested as an option and not as an explicit recommendation given the variability of evidence and the presence of side effects of systemic corticosteroid treatment. In AIED, corticosteroid therapy is the therapy of choice.

Rationale for therapeutic apheresis

Improvement of inner ear microcirculation and hair cell function by acute reduction of fibrinogen and cholesterol levels were the pathogenic mechanisms underlying the approach to use apheresis, in particular HELP-apheresis or rheopheresis as treatment for SSHL. Elevated fibrinogen and LDL cholesterol were identified as prognostic (Hira, 2021) and in former times as pathogenic factors at molecular levels. However, further analysis failed to confirm that thresholds should guide the indication for apheresis.

Two adequately powered multicenter RCTs, each enrolling more than 200 patients <7 days since onset of SSHL, evaluated HELP-apheresis (1 treatment) and rheopheresis (2 treatments) for SSHL (Mösges, 2009; Suckfüll, 2002). In the HELP-apheresis trial the control group received 250 mg prednisolone, tapered in 25 mg steps, 500 mL hydroxiethyl starch and 400 mg pentoxifylline for 10 days. In the rheopheresis trial the control group received either 250 mg methyl-prednisolone for 3 days with following stepwise reduction, or 500 mL hydroxyethyl starch plus 600 mg pentoxifylline for 10 days. Both trials could not demonstrate superiority in their apheresis arms after 48 hours or at 10 days. Another RCT ($n = 132$) investigated a single HELP-apheresis additional to 500 mL glycerol and 8 mg dexamethasone for 10 days (Bianchin, 2010). Statistically significant and clinically relevant hearing recovery was seen in standard treatment plus HELP group at 24 hours (75% vs. 41%) and 10 days (76% vs. 45%). Importantly the onset of SSHL in these patients was 12 to 13 days prior to treatment, thus reducing the amount or spontaneous recovery in enrolled patients. In patients who failed to respond to standard therapy, HELP-apheresis or rheopheresis demonstrated clinically significant improvement of hearing in >50%. The clinically relevant window of benefit spanned 6 weeks from the onset of SSHL (Heigl, 2009). Experience with TPE, or fibrinogen plasma adsorption is limited to very few patients. Including the last edition of the US guidelines, there is currently no international guideline of otolangological surgeons for SSHL mentioning apheresis explicitly as a therapeutic option.

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.

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Volume treated: TPE, HELP-apheresis, Rheopheresis: 1 TPV

Frequency: HELP-apheresis, Rheopheresis: 1 to 2 treatments; TPE, fibrinogen adsorption; 1 to 3; treatments performed on consecutive days or with 1-day intervals

Replacement fluid: TPE: albumin; none for selective methods

Duration and discontinuation/number of procedures

Procedures with all methods were mostly performed on consecutive days, depending upon response as determined by standard audiometry. There is no experience with increasing numbers of treatments over a longer period of time.

Keywords: plasma exchange, lipid apheresis, sudden sensorineural hearing loss, sudden deafness, rheopheresis, fibrinogen, tinnitus

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SYSTEMIC LUPUS ERYTHEMATOSUS

Incidence: 0.3 to 31.5/100,000 person-years				
Indication	**Procedure**		**Category**	**Grade**
Severe*	TPE		II	2C
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	1 (20)	2 (108)	>10 (>200)	NA

*Refractory and/or organ failure= diffuse alveolar hemorrhage, thrombotic microangiopathy, hyperviscosity, cryoglobulinemia, cytopenias, severe neuropsychiatric involvement and catastrophic antiphospholipid syndrome.

Description

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease of variable severity and course. Approximately 70% of patients with SLE follow a relapsing-remitting course, with the remaining 30% divided equally between prolonged remission and persistently active disease. The prevalence of SLE and organ manifestations vary considerably between different populations. Clinical symptoms are non-specific and/or attributable to the involvement of organ systems, in particular kidneys, heart, blood vessels, central nervous system, skin, lungs, muscles, and joints, leading to significant morbidity and increased mortality. Lupus nephritis (LN) affects 40% to 60% of patients, often as the initial manifestation. Nearly 10% of patients with LN will develop end stage kidney disease (ESKD). Considering the specific treatment of LN, there has been an increasing realization that for proliferative forms of LN (Class III/IV ± Class V) many patients may need less intense immunosuppression, especially with regard to glucocorticoid exposure, than previously thought. For patients with very severe proliferative LN, either histologically (abundant crescents, glomerular capillary necrosis) and/or clinically (rapid deterioration of kidney function), treating physicians may elect to use intense immunosuppression like in systemic disease. In the pathogenesis of SLE, both innate and adaptive immune responses are involved, with B cells being recognized as key mediators. Tissue damage is associated with autoantibodies or immune-complex depositions. Interaction of genes with environmental factors leads to numerous immunologic alterations that culminate into persistent immune responses against autologous nucleic acids. Low complement levels and high titers of autoantibodies suggests active disease. Screening tests include anti-dsDNA antibodies, antinuclear antibodies (ANA), antiphospholipid antibodies and complement levels. Autoantibodies reacting with the *N*-methyl-*D*-aspartate receptor are closely associated with neurocognitive impairment and fatigue in neuropsychiatric SLE. Persistent antiphospholipid antibodies and thrombotic or obstetrical events, such as recurrent pregnancy loss, may indicate a secondary antiphospholipid syndrome (APS; see Catastrophic antiphospholipid syndrome).

Current management/treatment

Treatment goals include long-term patient survival, prevention of organ damage and minimizing toxicities of therapy. Therapy should aim at remission or at least low disease activity and prevention of flares. Treatment of children should follow the same principles as in adult disease. Hydroxychloroquine is a first line treatment for almost all patients (Fanouriakis, 2021). Additional therapy entails immunosuppressive agents (glucocorticoids, azathioprine, methotrexate, cyclosporine, and mycophenolate mofetil). In persistently active or flaring disease, or organ-threatening refractory disease add-on belimumab and rituximab are used. Belimumab, targeting B cell-activating factor (BAFF) was the first biological approved for SLE by the FDA in 2011, which was extended for children ≥5 years in 2019, and specified for adult active LN in 2020. Anifrolumab (anti-type I interferon receptor antibody) was approved by FDA for moderate to severe SLE in 2021. Management recommendations may further change with more biologicals becoming available and being applied in the context of existing regimens.

Several scoring systems are available to determine disease activity and therapy efficacy in SLE. The SLE Disease Activity Index (SLEDAI) and the British Isles Lupus Assessment Group (BILAG) are the most frequently used in RCTs and observational studies. The SLEDAI consists of 24 items (present or absent) representing nine organ systems also scoring lupus serology. SLEDAI score >10 defines high disease activity. BILAG provides a comprehensive set of definitions for mild, moderate and severe activity in multiple organs, which requires an assessment of improved (1), the same (2), worse (3), or new (4) over the last month.

Rationale for therapeutic apheresis

TPE was initially used to treat SLE under the assumption that removing pathogenic autoantibodies and immune complexes would control disease activity. However, the first RCT in mild SLE, where the patients underwent six TPE within 2 weeks showed no clinical improvement (Wei, 1983). A RCT of TPE plus prednisone and cyclophosphamide versus prednisone and cyclophosphamide showed no benefit in the TPE arm (Lewis, 1992). In contemporary international guidelines for the management of LN (EULAR/ERA/EDTA/KDIGO) TPE is not among induction or maintenance therapies for LN but is mentioned as rarely indicated in situations of drug contraindications or refractory disease (Fanouriakis, 2020; Rovin, 2021). Pregnancy might be also considered in this context. The British Society for Rheumatology support the use of TPE as a treatment option for patients with severe, refractory disease manifestations (diffuse alveolar hemorrhage [DAH], thrombotic microangiopathy, hyperviscosity, cryoglobulinemia, cytopenias, severe neuropsychiatric involvement and catastrophic APS; Gordon, 2018).

Continuous publication of CRs and CS document unmet clinical needs in the treatment of SLE for which therapeutic apheresis is regarded as potentially effective option for escalating and/or adjuvant therapy in almost all facets of SLE. 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). In case reports of TTP associated with SLE, combination of TPE followed by rituximab or belimumab resulted in favorable outcome. There are data on use of IA and DFPP for severe refractory cases. A meta-analysis on 18 RCTs including 457 patients in

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China, overall showed clinical benefit of the use of IA for SLE treatment (Yang, 2020). However, preferential indications for TPE are not deducible from these results. A definition of refractory SLE would refer to underlying immunopathogenesis remaining unresponsive to a decent exposure of standard immunosuppressive drugs. The approval of biologicals and subsequent actual national implementation of use for routine care might substantially extend this definition.

Technical notes

Volume treated: 1 to 1.5 TPV

Replacement fluid: Albumin, plasma

Frequency: LN or DAH: daily or every other day; other severe disease conditions: 1 to 3 times per week

Duration and discontinuation/number of procedures

Typically, a course of 3 to 6 TPE is appropriate to see response in patients with refractory disease and/or severe complications of SLE. Prolonged treatments have been reported but efficacy and indication of this approach are questionable.

Keywords: systemic lupus erythematosus, lupus nephritis, neuropsychiatric lupus, plasma exchange, immunoadsorption

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SYSTEMIC SCLEROSIS

Incidence: 9 to 19/1,000,000/year

Procedure	Category		Grade	
ECP	III		2A	
TPE	III		2C	
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
ECP	3 (162)	0	5 (87)	NA
TPE	1 (15)	7 (132)	>10 (>200)	NA

Description

Systemic sclerosis (SSc) is a connective tissue disease characterized by the accumulation of collagen and other extracellular matrix proteins in skin, blood vessels, heart, lungs, kidneys, gastrointestinal (GI) tract, musculoskeletal system, and other organs. Skin fibrosis and associated Raynaud's phenomenon are prominent. There are two forms of SSc: diffuse cutaneous systemic sclerosis (dcSSc) and limited cutaneous systemic sclerosis (lcSSc). lcSSc presents with features of CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia), typically has slower disease progression but does have progression of disability and disfigurement over time. dcSSc is characterized by thickening of the skin (scleroderma) and progressive visceral organ dysfunction due to fibrosis, typically with rapid onset and decreased survival. Antinuclear antibodies are present in more than 95% of patients with SSc.

Current management/treatment

Routine management of SSc includes systemic therapies such as hydroxychloroquine, methotrexate, mycophenolate mofetil and cyclophosphamide, and symptom relief. The 2016 European League Against Rheumatism (EULAR) recommendations include: (a) SSc-Raynaud's phenomenon: dihydropyridine-type calcium antagonists, intravenous iloprost, and fluoxetine; (b) digital ulcers in SSc: intravenous iloprost, PDE-5 (phosphodiesterase type 5) inhibitors; bosentan, especially after treatment failure with calcium channel blockers, PDE-5 inhibitors or iloprost therapy; (c) SSc-PAH (pulmonary arterial hypertension): endothelin receptor antagonists, PDE-5 inhibitors or riociguat; intravenous epoprostenol for severe SSc-PAH; and prostacyclin analogues; (d) SSc skin and lung disease: methotrexate for skin manifestations of early diffuse SSc; cyclophosphamide, in particular for SSc with progressive interstitial lung disease; and hematopoietic stem cell transplantation for rapidly progressive SSc at risk of organ failure; (e) SSc renal crisis: ACE inhibitors, glucocorticoids, and plasma exchange in patients with microangiopathy or those intolerant to ACE inhibitors (Zanatta, 2018); (f) SSc-related gastrointestinal disease: proton pump inhibitor, prokinetic drugs and intermittent or rotating antibiotics. Other treatments have also been studied, including mesenchymal stem cell therapy, asiliximab, alemtuzumab, and abatacept.

Rationale for therapeutic apheresis

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 (Knobler, 2006). 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 (Rook, 1992). 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 (Enomoto, 1999). A CS of 16 patients treated with 12 ECP procedures (two consecutive days every 6 weeks) reported decreased dermal thickness and increased joint mobility (Papp, 2012). In a long-term follow-up study from the same group, those immunomodulatory effects of the ECP treatment last for 1 year only (Papp, 2016). The timing and indication for TPE and ECP in treating systemic sclerosis have not been well established.

TPE has been used for SSc with the rational that humoral factors might play an important role in the pathogenesis. 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 evaluated in a CT. All serological markers improved in comparison to the control group; however, there was no difference in clinical outcomes (Cozzi, 2001). In a CS reporting on 15 patients who received TPE in combination with prednisone and cyclophosphamide, 14 patients had clinical improvement (Dau, 1981). In a CS of scleroderma renal crisis in patients with microangiopathy or who were intolerant to high-dose ACE inhibitors, the addition of TPE preserved kidney function, decreased dialysis initiation, and improved 5-year survival rates (Cozzi, 2012). A comprehensive review analyzed 572 patients reported in the literature (including abstracts and non-English publications), of which 455 received TPE. This study reported that, after just 3 to 4 weekly treatments, most TPE-treated patients improved, particularly in Raynaud's symptoms and digital ulceration (Harris, 2018). A retrospective review of 8 patients with dcSSc who received therapy with glucocorticoid, cyclophosphamide, and double-filtration plasmapheresis showed significant improvement in skin scores over time. The frequency and number of TPE treatments was based on skin severity and varied among patients (Suga, 2020).

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Technical notes

Volume treated: ECP: varies. TPE: 1 to 1.5 TPV

Frequency: ECP: Two procedures within one week (one series) every 4 to 6 week for 6 to 12 months; TPE: 1 to 3/week

Replacement fluid: ECP: NA; TPE: albumin

Duration and discontinuation/number of procedures

For ECP, a 6-month trial may be considered. If no response is noted, ECP treatment intervals should be increased or stopped completely. TPE courses vary widely. A course of six procedures over the 2 to 3 weeks should constitute a sufficient therapeutic trial. Four weekly TPE treatments have been reported to result in long-lasting improvements in symptoms. 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) has also been used. In one study, TPE was discontinued when kidney function (Cr < 300 mmol/L and serum urea <15 mmol/L) remained stable for at least one month (Cr <300mmol/L and serum urea <15 mmol/L) or when the patient required dialysis (Cozzi, 2012).

Keywords: systemic sclerosis, scleroderma, CREST, plasma exchange, extracorporeal photopheresis

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THROMBOCYTOSIS

Incidence: ET: 0.2 to 2.5/100,000/year; PV: 0.2 to 2.3/100,000/year

Indication	Procedure		Category	Grade
Symptomatic	Thrombocytapheresis		II	2C
Prophylactic or secondary	Thrombocytapheresis		III	2C
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Symptomatic	0	0	10 (271)	NA
Prophylactic or secondary	0	0	3 (224)	NA

ET = essential thrombocythemia; PV = polycythemia vera.

Description

Thrombocytosis, defined as a circulating platelet count ≥450 × 10^9/L, is more commonly reactive (i.e., secondary thrombocytosis) to anemia (acute bleeding, hemolysis, or iron deficiency), infection, inflammation, asplenia, and/or malignancy. In these scenarios, the patient is not typically at increased risk of thrombosis or bleeding because, while elevated, the platelets are functionally normal. In contrast, with primary thrombocytosis, such as in myeloproliferative neoplasms (MPN), including essential thrombocythemia (ET), polycythemia vera (PV), chronic myeloid leukemia (CML), pre-fibrotic primary myelofibrosis (PMF), myelodysplastic syndromes, and rarely, acute myeloid leukemia, the platelets are functionally abnormal and thus, thrombocytosis can be associated with thrombohemorrhagic events.

ET is a clonal MPN characterized by autonomous overproduction of platelets. Most patients have mutations in *JAK2* (~55% of patients), calreticulin (*CALR*), or *MPL*, though up to 20% may be triple-negative. Arterial or venous thromboembolic events include microvascular thrombosis, stroke and transient ischemic attacks, myocardial infarction, venous thromboembolism, and first-trimester pregnancy loss (spontaneously or during an otherwise hypercoagulable state). The cumulative rate of thromboembolism is 1% to 3% per patient-year. Older age (>60 years), *JAK2* mutation, history of thrombosis, and/or cardiovascular risk factors are predictors of arterial thrombosis. ET can also lead to bleeding, which usually occurs in mucocutaneous sites (rarely GI) and affects 1% to 30% of patients, which is predominantly due to acquired von Willebrand syndrome (AVWS). Bleeding risk increases significantly when the platelet count is >1000 to 1500 × 10^9/L. Risk of hemorrhage and thrombosis also appears to be increased when the white blood cell count is elevated. If performed, splenectomy can be associated with extreme "rebound" thrombocytosis (>1000 × 10^9/L) in 5% of cases with postoperative thrombosis (10%) and bleeding (14%); however, platelet count does not predict thrombotic or hemorrhagic complications.

Current management/treatment

Low-dose aspirin is indicated for thromboprophylaxis in low-risk patients and may also alleviate vasomotor symptoms (e.g., headache, tinnitus, ocular disturbances, erythromelalgia). Low dose aspirin should not be used in patients with evidence of AVWS; however, it can be used if the von Willebrand factor ristocetin cofactor activity (VWF:RCo) is >30%. In high-risk patients, cytoreduction with hydroxyurea is indicated. Alternative therapies include interferon-α (treatment of choice in pregnancy), busulfan, and anagrelide, the latter of which is associated with an increased risk of post-ET myelofibrosis. Platelet count should be normalized before surgery, particularly splenectomy, to minimize complications and avoid rebound thrombocytosis. Thromboembolic events are treated in accordance with national guidelines and institutional policy. Patients with extreme thrombocytosis and thromboembolism or hemorrhage should be treated to lower the platelet count with medical therapy and/or thrombocytapheresis.

Rationale for therapeutic apheresis

Thrombocytapheresis has been used to treat acute and/or prevent recurrent thromboembolism or hemorrhage in selected patients with MPN and uncontrolled thrombocytosis. CRs describe rapid improvement of symptoms and thrombotic/hemorrhagic complications that are unresponsive to cytoreduction and other first-line therapies. It has also been used to treat extreme rebound thrombocytosis post-splenectomy and during pregnancy to prevent recurrent fetal loss in high-risk patients with MPN; it is not indicated or beneficial for standard-risk pregnancies. 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 in ET, which is particularly important for patients with AVWS and platelets >1000×10^9/L. Thrombocytapheresis is only a bridging therapy, therefore the use cytoreductive therapy is essential to prevent platelet rebound post-procedure.

Elective thrombocytapheresis should also be considered for patients at increased risk of major hemorrhage when hydroxyurea or other cytoreduction is contraindicated (e.g., pregnancy) or in situations when rapid reduction is necessary (e.g., urgent/emergent surgery). One CS described 185 patients with MPN who underwent single thrombocytapheresis procedures before starting aspirin and/or cytoreduction. The median reduction in platelet count was 45%, with greater efficiencies noted if baseline platelets were <1500 × 10^9/L (Nguyen, 2021). Another series of 81 patients with MPN with symptomatic thrombocytosis had a median platelet reduction of 26% and higher starting hematocrit (Jiang, 2021). Platelet-lowering agents must be given to prevent rapid re-accumulation of circulating platelets whenever possible. Although anecdotal CRs have described a potential benefit of thrombocytapheresis with secondary thrombocytosis, the rationale is undefined and efficacy unproven.

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Technical notes

Thrombocytapheresis is generally well tolerated. Each procedure lowers the platelet count by ~30% to 60%. Anticoagulant ratio (preferably with ACDA) should be 1:6 to 12; heparin should be avoided to prevent ex vivo platelet clumping.

Volume treated: 1.5 to 2 TBV

Frequency: Daily or as indicated to reach/maintain goal

Replacement fluid: Saline and/or albumin as necessary to maintain the blood pressure

Duration and discontinuation/number of procedures

With acute thrombohemorrhagic events, the goal is normalization of platelet count (i.e., $<400 \times 10^9$/L) and/or resolution of symptoms. It is important to maintain normal counts until cytoreductive therapy takes effect. Goal for prophylaxis of high-risk patients who are pregnant, undergoing surgery, or post-splenectomy should be determined on a 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 ≤ 450 to 600×10^9/L may be enough.

Keywords: thrombocytosis, essential thrombocythemia, myeloproliferative neoplasm, polycythemia vera, primary myelofibrosis, chronic myeloid leukemia, thrombocytapheresis

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THROMBOTIC MICROANGIOPATHY, COAGULATION MEDIATED

Incidence: rare (*THBD* 2%-5%, *DGKE* 3%)

Indication	**Procedure**		**Category**	**Grade**
THBD, DGKE, and *PLG* mutations	TPE		III	2C
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
THBD mutations	0	0	1 (6)	2 (2)
DGKE mutations	0	0	1 (4)	1 (1)
PLG mutations	0	0	0	1 (1)

DGKE = diacylglycerol kinase epsilon; PLG = plasminogen; THBD = thrombomodulin.

Description

Thrombotic microangiopathy (TMA) refers to endothelial damage and microthrombosis occurring in capillaries and arterioles. This can lead to microangiopathic hemolysis, thrombocytopenia, and ischemic end-organ damage, including kidney, heart, and neurologic involvement. Complement-mediated TMA (CM-TMA), also referred to as atypical hemolytic uremic syndrome (aHUS), is a rare condition most commonly due to loss-of-function genetic mutations of complement regulatory molecules, leading to uncontrolled activation of the alternative complement pathway (see Thrombotic microangiopathy, complement mediated). Additionally, genetic mutations in proteins of the coagulation cascade have been identified in patients presenting with apparent aHUS; however, the direct implications with respect to complement system dysfunction are unclear in these cases.

Thrombomodulin, *THBD*, is a thrombin cofactor that acts as an anticoagulant and decreases complement factor I (CFI)-induced C3b inactivation. Six different mutations in the *THBD* gene were found in 7 unrelated patients with clinical aHUS defined as ≥1 episode of TMA associated with kidney failure and without Shiga toxin (Delvaeye, 2009). These mutations impair the function of thrombomodulin and may account for ∼5% of the underlying genetic mechanism in patients with CM-TMA. The age range for affected patients with *THBD* mutations is 4 to 24 years. Patients with *THBD*-associated disease may have recurrent episodes and normal C3 and C4 levels. Diacylglycerol kinase epsilon (DGKE) is a lipid kinase that catalyzes phosphorylation of arachidonic acid containing phosphatidic acid to inhibit protein kinase C. Mutations may lead to a pro-thrombotic state. A study of 9 unrelated kindreds showed that mutations in *DGKE* were found in up to 50% of children presenting with apparent aHUS before 1 year of life and no patients after age 1 year (Lemaire, 2013). There have been other reports of patients with *DGKE* mutations presenting with TMA within the first year of life (Almoshary, 2017) though older children have also been diagnosed (Azukaitis, 2017). Plasminogen (PLG), the zymogen of plasmin, is a serine protease that dissolves fibrin. In 4 patients with clinical aHUS, four different *PLG* mutations have been found that suggest plasminogen deficiency and dysfunction. Some patients had more than one deleterious genetic mutation (e.g., *THBD* and *DGKE*). Other deleterious mutations found include factor mutations (e.g., FXII, c1681-1G>A and von Willebrand factor, c4165G>C, and others).

Current management/treatment

Initial management of coagulation-mediated TMA may differ from other aHUS 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 consistently benefit from eculizumab therapy, some having acute relapses while on the therapy (Lemaire, 2013; Azukaitis, 2017). Patients with combined mutations may benefit if there are associated complement mutations (Sanchez Chinchilla, 2014). Kidney transplantation may be efficacious in patients with *DGKE*, as relapses were not seen after transplant (in contrast to complement-mediated aHUS). Patients could also be considered for clinical trials if available.

Rationale for therapeutic apheresis

The benefit for TPE or plasma infusion is not consistent in this patient population. Further experience is needed to determine if plasma can be a source for therapeutic intervention, although intuitively, plasma should contain the deficient/absent or dysfunctional circulating coagulation factors. Of note, THBD is primarily a membrane-bound molecule, though circulating forms can be identified with similar activity (Loghmani, 2018). The largest CS included 13 patients with *THBD* mutation that were part of a larger aHUS registry review (Noris, 2010). Of these 13 patients, 6 patients were treated with plasma therapy (TPE or plasma infusion) for 8 separate episodes, with remission achieved in 7 episodes (88%; 5 complete and 2 partial remissions). One patient died and one went on to develop end stage kidney disease. The authors suggest no difference in plasma infusion compared to TPE, although this includes all patients with aHUS patients, not just patients with *THBD*.

Technical notes

The specific TPE replacement fluid strategy and frequency are not described. Recommendations are based on published reports to treat complement-mediated TMA.

Volume treated: 1 to 1.5 TPV

Frequency: Daily or every other day

Replacement fluid: Plasma

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Duration and discontinuation/number of procedures

As there is no standardized approach, the duration and schedule of TPE for treatment of thrombotic thrombocytopenic purpura has been empirically adopted in several patients, sometimes while diagnostic evaluation is ongoing. Based on final diagnosis, some patients may be transitioned to therapeutic complement inhibitors.

Keywords: coagulation, thrombotic microangiopathy, atypical HUS, thrombomodulin, diacylglycerol kinase episolon, plasminogen, *DGKE*, *THBD*, *PLG*

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THROMBOTIC MICROANGIOPATHY, COMPLEMENT MEDIATED

Incidence: 0.2 to 1.9 per million (all ages)

Indication	Procedure		Category	Grade
Factor H autoantibody	TPE		I	2C
Complement factor gene mutations	TPE		III	2C
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Factor H autoantibody	0	0	8 (217)†	NA
Complement factor gene mutations*	0	1 (31)	25 (406)†	NA

*Studies include some patients who were not tested or were tested and found negative for complement factor gene mutations; †one CS (Khandelwal, 2019) contributed Factor H autoantibody ($N = 74$) and other patients included under complement factor gene mutations ($N = 35$).

Description

Complement-mediated thrombotic microangiopathy (CM-TMA), also commonly called *atypical* hemolytic uremic syndrome (aHUS), is caused primarily by uncontrolled activation of the alternative complement system. It can manifest like infection-associated TMA, but may have a chronic, progressive course, punctuated by catastrophic events such as acute kidney injury, as well as neurologic, cardiac, gastrointestinal, respiratory, and other complications (Formeck, 2018). The rates of mortality and progression to end stage kidney disease (ESKD) are approximately 25% and 50%, respectively; however, rates may be improving with use of terminal complement inhibition (e.g., eculizumab). Milder presentations with little to no systemic/hematologic features, account for ~20% of cases. Disease may present with an insidious onset at any age, but many cases present in the first few months of life and 40% occur in young adults.

A growing list of genetic mutations and polymorphisms, primarily involving complement regulatory proteins, predispose to CM-TMA. The primary pathogenic event appears to be endothelial injury leading to formation of platelet-fibrin hyaline microthrombi, which occlude arterioles and capillaries. Approximately 60% of cases involve loss-of-function mutations of genes encoding complement regulators (e.g., complement factor H [*CFH*], membrane cofactor protein [*MCP*/*CD46*], and complement factor I [*CFI*]) or less commonly gain-of-function mutations of complement factor B (*CFB*) or C3 (*C3*). *CFH* mutations are the most frequent (20%-30%). *CD46* mutations are found in approximately 5% to 15% and *CFI* mutations in approximately 4% to 10%. Mutations of coagulation proteins (e.g., thrombomodulin, diacylglycerol kinase-Ɛ, and plasminogen) can also cause TMA (see Thrombotic microangiopathy, coagulation mediated) and account for ~5% of cases. Variants in *CFHR1* genes are often associated with acquired complement dysregulation due to anti-CFH autoantibodies, which occurs in 5% to 13% of patients. Penetrance of genetic forms is ~50%. Complement activating conditions, such as infection, pregnancy, autoimmune disease, transplantation, or drugs, may trigger clinical disease. A history of recurrent infections from *Streptococcus* or other encapsulated microorganisms such as *Neisseria meningitidis* or *Haemophilus influenza* may suggest a familial etiology. Diagnosis relies on: (1) lack of associated disease; (2) negative stool culture and/or PCR for Shiga toxin if presenting with diarrhea; and, (3) ADAMTS13 activity >10%, to exclude thrombotic thrombocytopenic purpura (TTP; see *separate fact sheet*). Of note, mutations are not identified in ~20% to 30% of patients.

Current management/treatment

Eculizumab, a humanized anti-C5 monoclonal antibody, blocks activation of the terminal complement cascade and is effective in patients with and without identified genetic mutations (Legendre, 2013). It is recommended by several guidelines as the first-line therapy for CM-TMA/aHUS. Empiric plasma therapy, either as TPE or plasma infusion (PI), is recommended while investigations for TTP and other forms of TMA are in progress, or if eculizumab is not available. Once other causes of TMA have been excluded, eculizumab should be initiated. A retrospective study of 31 adults observed better outcomes in patients treated with eculizumab and TPE/PI compared to those treated with TPE/PI alone (Cao, 2018). Rituximab and other immunosuppressive therapies may be initiated in combination with TPE if anti-CFH antibodies are identified. The data on the use of eculizumab in patients with anti-CFH antibodies is limited albeit promising. Kidney transplant risks recurrence of the disease process in the allograft. Liver transplant may be a curative therapy, but has been associated with high mortality risk. Ravulizumab, a longer acting version of eculizumab, has recently been approved for use in aHUS in several jurisdictions (Syed, 2021).

Rationale for therapeutic apheresis

Given the similar potential presentations, TPE should be initiated until TTP is ruled out. TPE with plasma replacement is thought to rebalance absent/defective circulating complement regulators and remove anti-CFH autoantibodies if present. The role of TPE in CM-TMA is becoming more limited with the availability of complement inhibition. A review of CRs of aHUS, published from 2005 to 2015, observed decreased mortality with eculizumab but not with use of TPE (Krishnappa, 2018). Retrospective analysis of pregnancy-associated aHUS (56% with complement gene abnormalities) found no difference in ESKD and chronic kidney disease in patients who did or did not receive TPE (Bruel, 2017). When eculizumab is not available, TPE/PI remains an alternative treatment option. Despite weak evidence, TPE is recommended as first line therapy for CM-TMA with identified anti-CFH antibodies; the combination of TPE and immunosuppression for antibody reduction has been shown effective. TPE has not be shown to influence outcomes in *MCP*/*CD46*-mutated CM-TMA, as the factor does not circulate in plasma. PI can be considered in patients for whom eculizumab and TPE are not available. A multicenter study did not observe

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differences in remission rates when patients were treated with PI versus TPE (Noris, 2010). A case series of 109 pediatric patients ($N = 74$ anti-CFH, $N = 35$ other aHUS) demonstrated reasonable short-term hematologic response and safety profile (Khandelwal, 2019).

Technical notes

As many affected patients are children, establishment of vascular access, circuit priming, and calcium supplementation are of special concern. More complications have been associated with extended use of TPE and filter reuse for membrane filtration procedures (Khandelwal, 2019). Use of solvent-detergent plasma as the replacement fluid of TPE has been reported.

Volume treated: 1 to 1.5 TPV **Frequency:** Daily

Replacement fluid: Plasma or 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. Duration or discontinuation of TPE should be based upon patient condition, response, and availability of eculizumab. When TPE is started before a diagnosis is established, it is important to obtain relevant laboratory testing such as PCR for Shiga toxin, ADAMTS13, and anti-CFH antibodies.

Keywords: atypical hemolytic syndrome, complement-mediated thrombotic microangiopathy, plasma exchange, thrombotic microangiopathy, complement

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THROMBOTIC MICROANGIOPATHY, DRUG INDUCED

Incidence: ticlopidine/clopidogrel: <1%; gemcitabine: ≤1%; quinine: rare

Indication	Procedure		Category	Grade
Ticlopidine	TPE		I	2B
Clopidogrel	TPE		III	2B
Gemcitabine/quinine	TPE		IV	2C
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Ticlopidine/clopidogrel	0	0	5 (174)	NA
Gemcitabine	0	0	5 (83)	20 (22)
Quinine	0	0	3 (32)	8 (8)

Description

Drug induced thrombotic microangiopathy (DI-TMA) is characterized by the development of TMA (microangiopathic hemolytic anemia, thrombocytopenia, and microvascular thrombosis) in association with exposure to a drug. Contemporary review articles use the general term DI-TMA to describe patients previously referred to as having both drug-induced hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). While several drugs have been reported to cause DI-TMA, the most implicated include: clopidogrel, calcineurin inhibitors (CNIs), estrogen/progesterone, gemcitabine, interferon, mitomycin, quinine, and ticlopidine. CRs have also implicated oxymorphone (containing polyethylene oxide), bevacizumab, carfilzomib, ixazomib, and palbociclib. Herbal remedies and illicit drugs are also potential causes of DI-TMA. Though many medications have been implicated as in DI-TMA, a minority have strong causal evidence to support the association. See Thrombotic microangiopathy, transplantation associated for discussion of TMA related to calcineurin inhibitors.

Current management/treatment

Initial management involves comprehensive medication review and immediate discontinuation of suspected drug, or reduction of dose when discontinuation is not an option given the patient's comorbidities. Supportive care and discontinuation may be sufficient for TMA resolution for some drugs. Other interventions may be needed and depend on the culprit drug, for example, gemcitabine (dialysis, antihypertensives, corticosteroids, eculizumab, rituximab), quinine (corticosteroids, antiplatelet agents), bevacizumab (corticosteroids, cyclophosphamide), cyclosporine/tacrolimus/sirolimus (use alternate immunosuppression). Eculizumab has been used in the setting of DI-TMA with success, even in patients in whom TPE has failed. A large CS found that patients with DI-TMA following allogeneic HSCT fared better with the use of eculizumab compared to TPE (Bohl, 2017). The use of TPE should be individualized, based on the mechanism of toxicity leading to the DI-TMA, especially with the availability and apparent efficacy of eculizumab. However, when TTP is clinically suspected, directed treatment including TPE should be undertaken while waiting for confirmatory diagnosis.

Rationale for therapeutic apheresis

The use of TPE is based on extrapolation of its effectiveness for immune-mediated TTP. However, unlike TTP, drug associated TMA is rarely associated with severe deficiency of ADAMTS13 levels or presence of inhibitors; in such cases, a diagnosis of drug induced or secondary TTP would be more appropriate (see Thrombotic microangiopathy, thrombotic thrombocytopenia purpura). Pathogenesis of DI-TMA is 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.

Two broad mechanisms for DI-TMA have been proposed, namely immune-mediated and non-immune (dose- or duration-dependent) causes; either may result ultimately in TMA. A detailed review of some of the most common causative drugs and the mechanisms by which they cause DI-TMA provides rationale as to why TPE may not be effective (Kreuter, 2012).

Some drugs may have specific patterns of presentation. Ticlopidine-induced TMA typically presents with ADAMTS13 activity severely diminished (<10%) with inhibitors present and should be managed as TTP. Most patients present >2 weeks after initial drug exposure and usually respond to TPE. TMA implicating clopidogrel usually has normal ADAMTS13 activity and presents ≤2 weeks after starting therapy. Most cases have mild hematologic presentation, marked kidney involvement, and are unresponsive to TPE. Gemcitabine-induced TMA in most cases is cumulative dose-dependent, though immune-mediated cases are described. ADAMTS13 activity is typically normal. In a literature review, among 26 patients not treated with TPE, 56% recovered from TMA, compared to 30% of 18 patients who received TPE (Glezerman, 2009). Another series compared 39 patients who received TPE to 59 who did not, without clear benefit in terms of survival and patients who received TPE experienced more hemorrhagic and bleeding complications (Daviet, 2019). In both series, however, the groups receiving TPE appeared to be more severely ill and more likely to have received dialysis. Quinine-induced TMA is confirmed to be immune-mediated. Of note, a CS from the Oklahoma TTP/HUS Registry described 19 patients with quinine-induced TMA who received TPE due to an initial concern for TTP, without clear benefit; 17 required dialysis, 14 went on to develop chronic kidney disease, and 9 patients died (Page, 2017).

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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 to 1.5 TPV **Frequency:** Daily or every other day

Replacement fluid: Plasma

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.

Keywords: drug induced thrombotic microangiopathy, plasma exchange, quinine, gemcitabine, bevacizumab, ticlopidine, clopidogrel, cyclosporine, tacrolimus, sirolimus, calcineurin inhibitors, mitomycin

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THROMBOTIC MICROANGIOPATHY, INFECTION ASSOCIATED

Incidence: STEC-HUS: 2 to 3/100,000 children <3 to 5 years; pHUS: <1/100,000 children <18 years

Indication	Procedure		Category	Grade
STEC-HUS, severe	TPE/IA		III	2C
pHUS	TPE		III	2C
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
STEC-HUS	0	2 (309)	NA	NA
pHUS	0	0	1 (6)	3 (3)

STEC-HUS = Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome; pHUS = *Streptococcus pneumoniae* hemolytic uremic syndrome.

Description

Hemolytic uremic syndrome (HUS) designates a heterogeneous group of disorders characterized by thrombotic microangiopathy (thrombocytopenia and mechanical hemolytic anemia) and predominant acute kidney injury. In 85% to 90% of children with HUS, the cause is due to the action of Shiga-like toxin (Stx) on the renovascular endothelium. This type of HUS is referred to as STEC-HUS, diarrhea-associated HUS (D+HUS) or *typical* HUS. Infection occurs through ingestion of contaminated food or water, person-to-person transmission, or contact with farm animals. STEC-HUS occurs most frequently in younger children, 2 to 10 days after a prodrome of bloody diarrhea caused by verocytotoxin (Stx)-producing bacteria. Prior to 2010, *E. coli* O157:H7 was predominantly isolated from patients with STEC-enteritis but currently non-O157 STECs are equally frequent in Europe and North America (O157 remains predominant in Latin America). STEC enteritis progresses to HUS in 5% to 10% of cases. In 2011, Europe experienced one of the largest recorded STEC-HUS outbreaks. A total of 3842 people were affected by a virulent and uncommon strain of enteroaggregative hemorrhagic *E. coli* (EAHEC) O104:H4. HUS developed in 855 (80% adults) with 54 deaths reported.

Stx has proinflammatory and prothrombotic effects on the vascular endothelium and may attach to and stimulate endothelial cells to release ultra-large von Willebrand factor multimers (ULVFWM) which directly activate complement or activate and promote platelet adhesion and aggregation. Stx also binds to multiple cells in the kidney and causes a spectrum of kidney injury, including vascular endothelial cell damage, thrombotic occlusion of the capillary lumen, glomerular endothelial cell swelling, glomerular and tubular cell apoptosis, and extensive cortical necrosis. Central nervous system (CNS) involvement occurs in up to 26% of children with STEC-HUS targeting brain endothelial and neuronal cells. The severity of acute illness, particularly CNS involvement and the need for dialysis, is strongly associated with worse long-term prognosis. Mortality is between 3% and 5% and up to 25% of patients may have long-term complications, including chronic kidney disease, proteinuria, and/or hypertension (Cody, 2019).

Of the remaining HUS cases in children, 5% to 15% result from *Streptococcus pneumoniae* sepsis or meningitis (pHUS) with the rest attributed to *atypical* HUS (see Thrombotic microangiopathy, complement mediated). pHUS mortality rates are as high as 50% and the pathogenesis is poorly understood. *S. pneumoniae*, as well as other bacteria and viruses, produce a ceramidase that cleaves cell surface glycoprotein sialic acid residues, exposing the Thomsen-Freidenreich (T-) antigen. Pathogenesis was historically attributed to binding of preformed IgM anti-T antibodies to exposed T-antigens on erythrocytes, platelets and endothelium; but newer insights suggest the involvement of complement dysregulation (Syed, 2019).

Current management/treatment

Supportive care is the mainstay of therapy for STEC-HUS and includes fluid management, treatment of hypertension and renal replacement therapy. Two multicenter RCTs showed no benefit of plasma infusions over supportive care (Rizzoni, 1988; Loirat, 1988). Short-term treatment with eculizimab and/or TPE/IA has been used in severe cases with life-threatening complications and lack of response to supportive care, although evidence supporting these therapies is limited (Fox, 2018).

For pHUS, early recognition and antibiotic treatment with supportive care is recommended. Since plasma normally contains antibodies directed against the Thomsen-Freidenreich (T-) antigen, which may worsen red cell agglutination, transfusion with plasma or unwashed red blood cells or platelets is generally avoided. There are case reports of successful use of eculizumab in select patients with pHUS (Bitzan, 2018).

Rationale for therapeutic apheresis

In STEC-HUS, TPE may reduce concentrations of various cytokines, ULVWFM and Stx that damage the endothelium; however, there are limited data to support this hypothesis. Free Stx has not been detected in the serum, and how it transits from the GI tract to target organs remains unclear. The largest case-control study examining TPE in STEC-HUS examined patients treated in the 2011 outbreak in Germany. TPE was performed in 251 patients yet evidence of benefit was not seen (Menne, 2012). However, in the same outbreak, TPE appeared to ameliorate the course in 5 adults in Denmark treated for acute kidney injury and CNS dysfunction (Colic, 2011). In Germany, in a prospective trial of 12 patients unresponsive to TPE or eculizumab, IA was safely used to rapidly ameliorate severe neurological deficits (Greinacher, 2011). One retrospective study from France had identified acute neurological involvement in patients with STEC-HUS, half of whom responded to TPE, suggesting some benefit in this specific clinical setting (Nathanson, 2010).

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For pHUS, TPE may remove antibodies directed against the exposed T-antigen, as well as circulating bacterial neuraminidase. Evidence supporting the use of TPE in pHUS is limited to CRs and one CS (Waters, 2007).

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 plasma and possible polyagglutination due to T-activation.

Volume treated: 1 to 1.5 TPV **Frequency:** Daily

Replacement fluid: STEC-HUS: plasma; pHUS: albumin

Duration and discontinuation/number of procedures

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

Keywords: hemolytic uremic syndrome, thrombotic microangiopathy, shiga toxin, *Streptococcus pneumoniae*, plasma exchange

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THROMBOTIC MICROANGIOPATHY, PREGNANCY ASSOCIATED

Incidence: pre-eclampsia in 2% to 7% of pregnancies; HELLP syndrome <1% of pregnancies

Indication	**Procedure**	**Category**	**Grade**
Pregnancy associated, severe*	TPE	III	2C
Extremely preterm** preeclampsia, severe	TPE/LA	III	2C

# reported patients: 100 to 300	**Procedure**	**RCT**	**CT**	**CS**	**CR**
Pregnancy associated, severe*	TPE	0	1 (55)	8 (53)	NA
Extremely preterm** preeclampsia, severe	LA	0	3 (58)	2 (9)	2 (3)
	TPE	0	0	2 (10)	1 (1)

HELLP = Hemolysis, Elevated Liver enzymes and Low Platelets; *failure to improve 24 to 72 hours postpartum or clinical concern for thrombotic thrombocytopenic purpura; **<28 weeks gestation.

Description

Thrombotic microangiopathy (TMA) is a pattern of endothelial injury that results in the clinical triad of thrombocytopenia, microangiopathic hemolytic anemia (MAHA) and organ injury. In pregnancy, TMA is diagnosed based on thrombocytopenia (platelets $<100 \times 10^9$/L), MAHA (hemoglobin <10 g/dL, lactate dehydrogenase (LDH) 1.5x upper limit of normal, undetectable haptoglobin, schistocytes on peripheral smear) and evidence of organ injury (kidney, heart, neurological). The differential diagnosis of TMA in the setting of pregnancy is broad and includes coagulation mediated TMA, complement mediated TMA (also referred to as *atypical* hemolytic uremic syndrome (aHUS)), drug associated TMA, infection associated TMA, thrombotic thrombocytopenic purpura (TTP; see *separate fact sheets*), pre-eclampsia and HELLP syndrome. Other clinical entities share overlapping features and should also be considered including antiphospholipid syndrome, systemic lupus erythematosus (SLE), acute fatty liver, immune thrombocytopenia (ITP), severe hypovolemic shock, sepsis, and sickle cell crisis.

Pre-eclampsia and HELLP syndrome are the most common causes of TMA during pregnancy and may represent a spectrum of disorders with HELLP being most severe. Severe pre-eclampsia is characterized by elevated blood pressure (≥140 mmHg systolic or ≥90 mmHg diastolic) and proteinuria (>300 mg/day) or at least one new severe feature after 20 weeks of pregnancy. HELLP syndrome designates the presence of hemolysis, low platelets, and liver dysfunction. In 70% to 80% of cases, HELLP coexists with pre-eclampsia but it can also occur in the absence of hypertension or proteinuria. Both pre-eclampsia and HELLP are associated with elevated levels of soluble fms-like tyrosine kinase 1 (sFlt-1), an anti-angiogenic protein that causes vasoconstriction and endothelial damage. Measurement of a sFlt-1/placental growth factor (PlGF) ratio of >85 before 34 weeks or >100 after 34 weeks supports the diagnosis (Fakhouri, 2020) and is associated with adverse pregnancy outcomes. Levels of sFLT-1 rapidly decline after delivery and prompt delivery is the definitive treatment for pre-eclampsia and/or HELLP with most cases improving within a few days of delivery (Zununi Vahed, 2021).

Individuals who develop HELLP have a high risk of recurrence in subsequent pregnancies (14%-24%). Both pre-eclampsia and HELLP seem to involve complement activation and decreased complement regulation with complement gene deletions and variants detected in a subset of patients (Burwick, 2020). There are case reports of patients with pre-eclampsia and HELLP who have responded to treatment with eculizumab (Elabd, 2019; Lokki, 2020).

Since TMA in the setting of pregnancy has a broad differential that includes TTP, prompt treatment with plasma exchange should be initiated when TTP is suspected. ADAMTS-13 testing can help clarify the situation and guide therapy. TTP in pregnancy is suggested by ADAMTS-13 levels <20% with or without the presence of anti-ADAMTS-13 antibodies. In contrast to TTP, ADAMTS-13 levels in pre-eclampsia and HELLP are typically low but detectable (20%-50%) and autoantibodies against ADAMTS13 are not present (Fakhouri, 2020).

Current management/treatment

Prompt delivery, generally by cesarean section, is the definitive treatment for pre-eclampsia and HELLP. Steroids are used to support fetal lung maturity in pre-term cases. Additional supportive therapies include hypertension management and parental magnesium therapy for seizure prophylaxis.

Rationale for therapeutic apheresis

TPE lowers circulating sFlt-1 levels and may remove other causative agents that have not yet been identified (Gubensek, 2021). Multiple CRs, CS, and one retrospective CT (Eser, 2005), have shown clinical benefit of TPE in post-partum pre-eclampsia and HELLP (persisting >48 hours after delivery). However, many of these studies did not include ADAMTS-13 measurements to rule out TTP and may have included patients who had TTP. One small study, which used ADAMTS-13 levels to differentiate HELLP from TTP, showed recovery in 4 severe HELLP cases treated with high dose steroids without the use of TPE (Pourrart, 2013).

Currently, TPE is recommended in patients with suspected pre-eclampsia/HELLP who have severe thrombocytopenia and life-threatening neurological or cardiac signs (seizures, coma, altered mental status, elevated troponins) until TTP is ruled out with an ADAMTS-13 level of greater than 20%. TPE can be considered in other patients whose thrombocytopenia, hemolysis and kidney function fail to improve 24 to 72 hours after delivery until diagnostic workup is completed, including ADAMTS-13 level and sFlt-1/ PlGF ratio drawn before plasma is exchanged. Once all alternative diagnoses are excluded, treatment for complement mediated TMA/aHUS with an anti-C5 agent such is eculizumab is recommended (Fakhouri, 2020). Antepartum TPE for suspected HELLP remains a category IV indication as described in the JCA 2019 Special Edition, as prompt delivery is the definitive treatment.

Regarding the use of selective methods of therapeutic apheresis to prolong pregnancy in extremely preterm pre-eclampsia, there are two competing approaches. One group hypothesizes sFlt-1 is a causal risk factor rather than only a risk marker for pre-eclampsia (Thadani, 2011; Thadani, 2016). In

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their studies, they used the dextran-sulfate (DSA) full blood adsorber, which is a standard method for LA in Europe. Mean sFlt-1 levels were reduced by only 18% (range 7%-28%). Therefore, a proof of concept is needed which is ongoing in the United Kingdom (NCT02923206) using an experimental sFlt-1-specific adsorber. Another group used HELP-apheresis, which is also in routine use for lipoprotein apheresis; however, this method does not remove sFlt-1 (Winkler, 2018). This group hypothesizes altered lipoprotein metabolism may impair endothelial and placental function in pre-eclampsia. A pilot study presented first results with HELP-apheresis (Wang, 2006). Both groups demonstrated prolongation of pregnancy from the day of admission to the hospital with a few (range 1-6) DSA-full blood adsorption or HELP-apheresis treatments (Thadani, 2016; Winkler, 2018). Currently, TPE is considered to be equally effective with wider availability and fewer side effects, but more studies are needed before this approach is widely adopted.

Technical notes

Volume treated: 1 to 1.5 TPV

Frequency: Daily if there is no improvement at 24 to 72 hours 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 as per TTP.

Keywords: pre-eclampsia, HELLP syndrome, hemolysis, elevated liver enzymes, low platelets, pregnancy, thrombotic microangiopathy, plasma exchange, lipoprotein apheresis

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THROMBOTIC MICROANGIOPATHY, THROMBOTIC THROMBOCYTOPENIC PURPURA

Incidence: <1/100,000/year				
Procedure	**Category**		**Grade**	
TPE	I		1A	
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	7 (301)	5 (270)	NA	NA

Description

Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy (TMA) characterized by the development of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and ischemic organ dysfunction associated with a severe deficiency of plasma ADAMTS13 activity, with levels lower than 10% in most cases. It can be associated with varying degrees of neurologic manifestations (e.g., headache, mental status changes, TIA), kidney involvement, fatigue/weakness, and fever. Because TTP is potentially fatal if left untreated (~90% mortality), there should be a low threshold to initiate treatment for presumed TTP within 4 to 8 hours of diagnostic suspicion, after other causes of systemic TMA have been considered unlikely, and without waiting for the results of ADAMTS13 testing. Scoring systems can be used to determine pre-test probability for TTP while awaiting confirmatory ADAMTS13 testing (Benhamou, 2012; Bendapudi, 2017). The PLASMIC scoring system includes 7 independent variables identified as highly predictive by multivariable regression including platelet count $<30 \times 10^9$/L, creatinine <2.0 mg/dL, international normalized ratio (INR) <1.5, mean corpuscular volume (MCV) <90 fL, and hemolysis (Bendapudi, 2017).

Most patients have immune-mediated TTP which develops due to autoantibodies (usually IgG) against ADAMTS13, whereas congenital TTP comprises the minority of cases and is associated with germline mutations resulting in severely deficient ADAMTS13 function. Despite successful treatment of immune-mediated TTP, the disease can recur. IgG4, the most common anti-ADAMTS13 IgG subclass, appears to be related to disease recurrence.

Current management/treatment

TPE has decreased overall mortality of immune mediated TTP from nearly uniformly fatal to <10% to 20%. TPE should be initiated emergently once the diagnosis is suspected. If TPE is not immediately available, large dose plasma infusions (25-30 mL/kg), should be given if tolerated, until TPE can be initiated (Coppo, 2003). Corticosteroids should be used as an adjunct, either a daily prednisone dose at 1 mg/kg/day, pulsed methylprednisone for a few days, or a combination; however, no definitive trials proving their comparative efficacy have been performed. Rituximab, previously used to treat refractory or relapsing TTP, is now often added as adjunctive agent with initial TPE and corticosteroids. A meta-analysis of 570 patients demonstrated that the addition of first-line rituximab, offered high efficacy for the prevention of relapse and lower mortality rate in cases of acquired TTP, compared with conventional therapy alone (Owattanapanich, 2019). Rituximab has allowed for tapering steroids rapidly (over 3-4 weeks). Since rituximab immediately binds to CD20-positive lymphocytes, an 18 to 24-hour interval between its infusion and TPE is used in practice.

Caplacizumab, a nanobody directed against the platelet binding domain (A1) of VWF, has been approved for the treatment of immune TTP together with TPE. When added to TPE plus immunosuppression in a phase II placebo-controlled RCT it induced a significantly faster resolution of acute TTP episode (Peyvandi, 2016). HERCULES, a phase III randomized, double-blind, placebo-controlled study demonstrated that patients with acquired TTP receiving caplacizumab were 1.5x more likely to normalize platelet count and had a 74% lower risk of a composite of TTP-related death, recurrence, or a major thromboembolic event while undergoing treatment compared to those patients receiving placebo (Scully, 2019). While it is hypothesized that refractory TTP will be less common in the era of caplacizumab, in relapsed or refractory cases cyclosporine A, bortezomib, cyclophosphamide, azathioprine, vincristine, N-acetylcysteine or splenectomy can be considered. Novel agents, such as recombinant ADAMTS13, and inhibitors of the VWF-glycoprotein Ib/IX interaction (anfibatide) are currently under investigation and show promise for the treatment of TTP. Long-term follow-up after the acute episode is critical to monitor for relapse and to diagnose and manage chronic sequelae of this disease.

Patients with TTP have a thrombotic rather than hemorrhagic tendency and bleeding, if present, is typically limited to skin and mucous membranes. Platelets should only be transfused if potential life-threatening bleeding is present. Because congenital TTP is characterized by constitutive deficiency of ADAMTS13 activity without an inhibitor, simple infusions of plasma (10-15 mL/kg) or cryosupernatant or plasma derived VWF concentrates have been used.

With the advent of the COVID-19 pandemic, postvaccination-related TTP has been reported. This is distinct from Vaccine-induced immune thrombotic thrombocytopenia (VITT; see *separate fact sheet*). In a systematic review of 27 reported cases, most episodes of postvaccination-related TTP were seen after BNT162b2 vaccine, followed by mRNA-1273 vaccine. Some patients had no prior history of TTP while others had relapsed immune TTP, and one patient had relapsed congenital TTP. The mean onset of symptoms post-vaccination was 13.4 days. ADAMTS13 activity ranged from 0% to <12%. All patients with immune TTP except one received TPE and steroids. Twelve patients received caplacizumab, and 17 patients received rituximab, while the patient with congenital TTP received plasma infusion. Only one patient had a relapse within 30 days after discharge from the hospital. One patient passed away after two days of hospitalization, likely due to a sudden cardiovascular event (Saluja, 2022). CRs of immune TTP following COVID-19 infection have also been reported.

Rationale for therapeutic apheresis

TPE with plasma replacement has significantly improved patients' clinical outcomes. Where available, solvent-detergent plasma products may reduce allergic symptoms. The proposed mechanism of TPE is that it provides adequate levels of ADAMTS13 protease activity while removing circulating anti-ADAMTS13 autoantibodies. However, clinical course does not always correlate with plasma ADAMTS13 activity or ADAMTS13 inhibitor levels.

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Technical notes

Allergic reactions and citrate reactions are more frequent due to 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.

Volume treated: 1 to 1.5 TPV **Frequency:** Daily

Replacement fluid: Plasma or plasma/albumin

Duration and discontinuation/number of procedures

TPE is generally performed daily until the platelet count is >150 × 10^9/L, and LDH is near normal for 2 to 3 consecutive days. Residual schistocytes after discontinuation of daily TPE are not uncommon and after the initial diagnosis of TTP is made, there is no reason to continue documenting the presence or absence of schistocytes. There are no RCTs of TPE over longer duration. A small retrospective study had suggested a lower overall recurrence rate at 6 months with taper. A common taper strategy is three times a week for the first week, twice weekly the second and then once weekly the following week(s). Other taper approaches have been documented. However a prospective observational investigation found that tapering TPE (when compared to an historical cohort of no TPE taper), did not reduce exacerbation in patients with TTP (Raval, 2020).

Keywords: thrombotic thrombocytopenic purpura, thrombotic microangiopathy, plasma exchange

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THROMBOTIC MICROANGIOPATHY, TRANSPLANTATION ASSOCIATED

Incidence: 10% to 40% in allogeneic hematopoietic stem cell transplantation

Procedure	**Category**		**Grade**	
TPE	III		2C	
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Post-HSCT	0	0	>10 (>200)	NA

Description

Thrombotic microangiopathy (TMA) following hematopoietic stem cell transplantation (HSCT) or solid organ transplantation (SOT), also referred to as transplant associated TMA (TA-TMA), is a potentially severe complication. While the underlying pathophysiology of TA-TMA is complex, research has demonstrated three main pathways of injury: (1) chemotherapy and medications damage endothelial cells, leading to a pro-coagulant state; (2) activation of antigen presenting cells and lymphocytes; and (3) activation of the complement cascade culminating in microthrombi formation (Dvorak, 2019). Unlike thrombotic thrombocytopenic purpura (TTP; see *separate fact sheet*), plasma ADAMTS13 protease levels are not severely deficient nor is ADAMTS13 inhibitor activity detectable. The incidence of TA-TMA is 10% to 40% in patients with allogenic HSCT, but is less commonly described after SOT. Kidneys are the major target organs affected, but the central nervous system, pulmonary, gastrointestinal and serosa may also be involved. Diagnosis can be made histologically, but non-invasive laboratory criteria include microangiopathic hemolytic anemia with high lactate dehydrogenase (LDH) and low haptoglobin, thrombocytopenia, schistocytes on blood smear, hypertension, proteinuria (random urine protein and creatinine should be measured; protein:creatinine ratio >2 is considered abnormal), and evidence of terminal complement activation with an elevated plasma concentration of sC5b-9 (significant elevation of this marker typically predicts poor outcome). A high index of suspicion is needed as anemia, thrombocytopenia, and increased creatinine are not uncommon post-HSCT; therefore routine weekly screening for LDH, proteinuria, and haptoglobin is useful. In patients with new transfusion requirements, elevated LDH, proteinuria, low haptoglobin, and hypertension, a diagnosis of TA-TMA should be strongly considered. TMA can occur within the first few weeks following transplant or as a late complication (up to 8 months). The mortality rates in patients who develop severe TA-TMA is >80%. One study suggests early detection and initiation of directed treatment with complement blockade may preserve end organ function and overall outcomes (Jodele, 2018).

Current management/treatment

No universal care strategies for TA-TMA exist. Initial management is mostly supportive and includes tight control of blood pressure, treatment of co-existing infections, and management of GVHD. Reduction or discontinuation of mTOR and calcineurin inhibitor drugs should be considered in the absence of GVHD, however, these decisions to change immunosuppression must be made on an individual basis. With increasing data regarding the involvement of complement dysregulation in patients with TA-TMA, the complement-inhibiting monoclonal antibody eculizumab has been used with success, especially in patients in whom therapy is initiated early in the disease process. One study compared patients with TA-TMA having received eculizumab to historical patients receiving conventional therapy. Despite a very good response in the eculizumab-treated group, there was no significant improvement in overall survival, due primarily to a high rate (70%) of infection-related mortality (Bohl, 2017). Other treatment options include rituximab, defibrotide, IL-2 receptor antibodies, pravastatin, and TPE. A longer acting complement-inhibiting monoclonal antibody, raviluzumab, is being investigated in clinical trials to assess efficacy in children and adolescents following HSCT.

Rationale for therapeutic apheresis

The use of TPE is based on extrapolation of its effectiveness for TTP. Therapeutic rationale is undefined and consistent with the uncertain clinical efficacy. No RCTs have addressed the efficacy of TPE for TA-TMA. CSs have reported overall response rates with TPE (usually after drug withdrawal) ranging from 0% to 72%, but with frequent partial responses with subsequent relapses, and up to 15% procedural adverse events. In addition, patients often receive multiple treatments which limits the ability to separate out clearly the effect of TPE. One CS in which 82 patients underwent TPE as primary therapy for TA-TMA had an overall response of 52% (4 patients with complete response, 39 with partial response). Additional therapies included rituximab ($n = 11$), rituximab + eculizumab ($n = 1$), defibrotide ($n = 1$). Only 20% of patients survived, with the highest risk of failure associated with gastrointestinal bleeding, severe aGVHD grades 3 to 4, severe anemia, and lower volume TPE (Yang, 2022).

Despite the poor efficacy of TPE overall, patients who present with TA-TMA more than 100 days after HSCT may have better outcomes and lower mortality (Mulay, 2015). A retrospective study in 15 patients demonstrated that treatment with at least 7 weeks of TPE did not prevent the development of chronic kidney disease in patients with TA-TMA (Sartain, 2019). Because some patients responded to TPE, a trial could be considered as salvage therapy for select patients with persistent or progressive TA-TMA despite resolution of infections and GVHD. In children with TA-TMA there is some evidence that very early initiation of TPE might be beneficial, even in patients with multiorgan failure.

TMA can also be a rare but serious complication following SOT and may be associated with calcineurin inhibitor and mTOR inhibitor use. It is associated with a high degree of morbidity or mortality and can result in loss of the graft. The value of TPE following SOT remains controversial, but small CS are published (Thomas, 2021). Complement blockade with eculizumab is also utilized.

Technical notes

TPE for patients with TA-TMA is often complicated by thrombocytopenia, anemia and co-morbidities related to GVHD and infections, including bleeding and hypotension. Therefore, the pattern of platelet and LDH responses may be variable and incomplete compared to patients undergoing TPE for TTP. This may make a therapeutic endpoint difficult to determine. ACD-A should be used as anticoagulant in patients with bleeding risk.

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Volume treated: 1 to 1.5 TPV **Frequency:** Daily, or as needed for chronic management

Replacement fluid: Plasma or plasma/albumin

Duration and discontinuation/number of procedures

TPE is usually performed daily until a clinical response is achieved and then either discontinued or tapered off, similar to treatment for TTP.

Keywords: thrombotic microangiopathy, hematopoietic stem cell transplantation, transplantation-associated thrombotic microangiopathy, plasma exchange

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THYROID STORM

Incidence: rare				
Procedure	**Category**		**Grade**	
TPE	II		2C	
# reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
	0	0	>10 (>200)	NA

Description

Hyperthyroidism is characterized by increased thyroid hormone synthesis and secretion from the thyroid gland, whereas thyrotoxicosis refers to the clinical syndrome of excess circulating thyroid hormones, irrespective of the source. Thyroid storm is an extreme manifestation of hyperthyroidism. Amiodarone-associated thyrotoxicosis, diffuse toxic goiter (commonly known as Graves' disease), and autoimmune thyroiditis are the main causes of this rare and serious complication requiring intensive care. Toxic multinodular goiter or solitary toxic adenoma are less frequent causes. The cause of diffuse toxic goiter is thought to be multifactorial, arising from the loss of immunotolerance and the development of autoantibodies that stimulate thyroid follicular cells by binding to the thyroid stimulating hormone (TSH) receptor. The exact mechanism underlying the subsequent development of thyroid storm from uncomplicated hyperthyroidism is not well understood. A common hypothesis for this condition is the presence of both larger availability of adrenergic receptors and a reduction of thyroid hormone binding to thyroid hormone binding globulin (TBG); these result in leaking catecholamines to precipitate thyroid storm.

Thyroid storm is an emergency with a mortality rate up to 25%. Symptoms are frequently 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. Patients with preexisting hyperthyroidism that had been partially or untreated are also at higher risk. The clinical picture is one of severe hypermetabolism and systemic decompensation (e.g., fever, tachycardia and arrhythmias, congestive heart failure, tremulousness and restlessness, delirium or frank psychosis, nausea, vomiting, abdominal pain, and, as the disorder progresses, encephalopathy, hypotension, acute ischemic stroke, and multi-organ failure). Hence, this clinical picture in a patient with a history of preexisting thyrotoxicosis, with goiter or exophthalmos, is sufficient to establish the diagnosis. Burch and Wartofsky created a scoring system to help standardize diagnosis using body temperature, central nervous system involvement, gastrointestinal-hepatic dysfunction, heart rate, and the presence or absence of congestive heart failure and/or atrial fibrillation. When a clinical diagnosis is made, emergency treatment should be initiated prior to laboratory confirmation. Serum T3 or T4 concentration cannot differentiate between severe thyrotoxicosis and thyroid storm. SOFA score or cardiogenic shock within 48 hours after intensive care unit (ICU) admission were independently associated with in-ICU mortality irrespective of treatment modalities in a retrospective multicenter study of 92 patients (Bourcier, 2020).

Current management/treatment

A multimodal treatment approach is highly recommended, which includes anti-thyroid drugs to stop thyroid hormone synthesis (i.e., propylthiouracil [PTU], methimazole, thiamazole, and carbimazole) and release (iodine), blocking T_4 to T_3 conversion (glucocorticoids), inhibiting the enterohepatic circulation of thyroid hormone (cholestyramine), controlling the peripheral effects of the thyroid hormones (ß-blockers), managing high fever, and overall hemodynamic stabilization. If a precipitating event is present, then it should also be treated concurrently. The order of treatment is important. PTU or thiamazole are preferred drugs in diffuse toxic goiter. The exceptions are during the first trimester of pregnancy, when PTU is preferred, and in patients with adverse reactions to thiamazole. Thiamazole has several advantages over PTU, such as better efficacy, longer half-life and duration of action, allowing once-daily dosing. Controlling the cardiovascular manifestations of thyroid storm is vital, large doses of ß-blockers might be required. Aspirin or other salicylates should not be used because they increase serum hormone levels.

Rationale for therapeutic apheresis

Both TPE and emergency surgery have been used to treat thyroid storm in patients who respond poorly to first line therapeutic measures. TPE is usually performed in patients with thyroid storm with severe symptoms and when the patient does not improve with first-line therapies within 24 to 48 hours of treatment or when first-line therapies cannot be used due to toxicity, such as leukopenia due to antithyroid drugs. Since a portion of T_3 and T_4 is firmly bound to plasma proteins, TPE should efficiently reduce their circulating pool with resulting decrease in hormone concentrations. In a review of the literature, TPE decreased the levels of free T4 and T3, and total T3 and T4 significantly (Garla, 2018). 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. The therapeutic benefit of TPE can be achieved by 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 the hormone levels typically rise again the next day. Continuous dialysis modalities, for example, with albumin containing dialysate, were experimentally used to increase thyroid hormone clearance. If removal of autoantibodies is considered for stabilizing the therapeutic result, in particular with associated ophthalmopathy, selective apheresis methods like IA or DFPP have been used.

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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 and thus, decreasing the free thyroid hormone concentration.

Volume treated: 1 to 1.5 TPV

Replacement fluid: Plasma, albumin

Frequency: Daily to every 3 days, with monitoring of thyroid hormone levels, and guided by control of systemic symptoms

Duration and discontinuation/number of procedures

TPE should be continued until clinical improvement is noted. Usually 3 to 6 procedures with a range upto >10 are performed to achieve clinical stabilization, potentially bridging to thyroidectomy.

Keywords: hyperthyroidism, plasma exchange, plasmapheresis, thyroid storm, thyrotoxicosis

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TOXIC EPIDERMAL NECROLYSIS

Incidence: 2/1,000,000/year				
Indication	**Procedure**		**Category**	**Grade**
Refractory	TPE		III	2B
# reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
	0	1 (35)	>10 (>200)	NA

Description

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), also called Lyell syndrome, represent a spectrum of severe idiosyncratic reactions characterized by mucocutaneous lesions leading to necrosis and sloughing of the epidermis. Eye involvement may occur in 80% of patients, and other organs, including the liver, kidney, lungs, and gastrointestinal tract can be involved. Medications are the most common trigger, however, other etiological factors include mycoplasma, viruses, and vaccines. There have been several published reports of TEN associated with COVID-19 infection, however, the majority, in adults, were probably associated with medication used for treatment. SJS/TEN has also been documented following COVID-19 vaccination. 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 to 4 weeks in medication-related cases and is rarely more than 8 weeks. Upon re-exposure, symptoms may recur in as little as 48 hours. 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 within 1 to 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% to 3%, while mortality for TEN is 25% to 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 associated between the HLA-B*1502 allele and carbamazepine induced TEN.

Current management/treatment

For medication-induced SJS/TEN, the causative medication must be 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. TEN is managed by supportive care in an intensive care unit or burn center, and includes skin care, fluid and electrolyte management, nutritional support, eye care, temperature management, appropriate analgesia, and treatment of infections. Fluid and electrolyte losses may occur due to the extensive mucocutaneous lesions. Patients with TEN are at high risk for infection, and sepsis is the 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. Treatment may include one or a combination of medications (glucocorticoids, cyclosporine, etanercept), IVIG and TPE. Two large meta-analyses of nearly 100 studies have suggested a promising survival benefit with the use of glucocorticoid and cyclosporine (Zimmerman, 2017; Houschyar, 2021). One retrospective study demonstrated that high-dose steroid administration with or without TPE and/or IVIG was associated with a lower mortality rate (13.6% vs. 24.0%) predicted by the SCORTEN based on the analysis of patients with TEN treated with supportive care alone (Watanabe, 2021). A metanalysis and metaregression of observational studies in TEN suggested that of the interventions reviewed, the lowest mortality rate was associated with treatment using etanercept or steroids whereas the highest mortality rate was observed in those patients that received TPE and TPE + IVIG (Krajewski, 2022). This mortality was higher than supportive care alone. It was noted, however, that patients in these studies receiving TPE and/or IVIG did have a higher SCORETEN. The same author group reviewed their 10-year experience of using simultaneous TPE and IVIG to control the disease. Twenty-eight patients receiving both TPE and IVIG were compared to 7 patients that received a single therapy treatment. The mortality in the test group was 14.29%, and the difference reached statistical significance ($P<.05$) in comparison with the single therapy group (Strużyna, 2022).

Rationale for therapeutic apheresis

The rational supporting TPE in TEN includes removal of drug/drug metabolites, cytokines, or other mediators of keratinocyte cytotoxicity. At least one report has demonstrated decreased levels of serum cytokines following TPE (Narita, 2011). TPE is typically not used in patients with SJS.

Numerous uncontrolled CRs and CS have noted use of TPE in the setting of severe cases of TEN refractory to standard treatment. Given the significant 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. Most reports describe application of TPE in combination with other therapies.

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Technical notes

While most reports have utilized TPE to treat refractory TEN, some groups from Japan have also used DFPP.

Volume treated: 1 to 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/ocular lesions, or evidence of skin healing.

Keywords: Stevens-Johnson syndrome, toxic epidermal necrolysis, plasma exchange

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TRANSPLANTATION, HEART

Incidence: cellular rejection ~21% to 30% in 1st post-transplant year

Indication	Procedure		Category	Grade
Cellular rejection/Recurrent rejection	ECP		II	1B
Rejection prophylaxis	ECP		II	2A
Desensitization/Rejection prophylaxis	TPE		II	1C
Antibody mediated rejection	TPE		III	2C
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Cellular/Recurrent rejection	0	1 (235)	4 (58)	NA
Rejection prophylaxis	1 (60)	2 (38)	2 (30)	NA
Desensitization/Rejection prophylaxis	0	7 (934)	NA	NA
Antibody mediated rejection	0	0	>10 (>200)	NA

Description

Heart transplantation remains the gold standard for treatment of advanced heart failure refractory to medical therapies. Significant advances in the field of solid organ transplantation, including advancements in immunosuppression (IS), have significantly enhanced survival and quality of life for heart transplant patients. However, increased IS generally leads to increased risks of opportunistic infection, secondary malignancy, metabolic derangement, and end organ damage. Episodes of allograft rejection continue to threaten long-term graft survival. Compliance with IS does not alleviate the risk of acute or chronic rejection which may lead to heart failure, need for second transplant, or death. Heart allograft rejection may be hyperacute (in cases of ABO or major HLA incompatibility), acute antibody mediated rejection (AMR), acute cellular rejection (ACR, most common), or chronic rejection (allograft vasculopathy). ACR is mediated through T cells, while AMR is mediated by antibodies directed against the allograft or donor specific antibodies (DSA). Patients experiencing AMR are more likely to experience hemodynamic instability secondary to decreased heart function. AMR has a poorer prognosis than ACR and is associated with the early development of allograft vasculopathy. Young age, history of congenital heart disease, high titer of human leukocyte antigen (HLA) antibodies, positive pre-transplant crossmatch, sensitization to muromonab-CD3, or prior cytomegalovirus exposure increases the risk of AMR in these patients.

Current management/treatment

Rejection is treated with immunosuppressive medications. Steroids are often first line therapy. If AMR progresses, rituximab, eculizumab, IVIG, ECP, and TPE are considered. Desensitization and rejection prophylaxis regimens are variable and may include TPE or ECP.

Rationale for therapeutic apheresis

Highly sensitized patients in need of heart transplantation face challenges in obtaining a compatible allograft. Apheresis techniques in combination with IS have been tested in desensitization, AMR prophylaxis, and rejection protocols. ECP reduces production of effector T-cells while expanding Tregs (CD4+/CD25+/Foxp3+) which suppress the immune system in an antigen-specific fashion and induces plasmacytoid (tolerogenic) dendritic cells. ECP therapy does not increase infection risk, but may require placement of a central venous catheter with its own complications of bleeding, infection, and thrombosis to consider. ECP has been shown to improve outcome after recalcitrant/severe rejection following heart transplantation. In one study, ECP treatment in 36 patients significantly decreased rejection (Kirklin, 2006). In an RCT comparing ECP versus non-ECP in the prevention of rejection, episodes of acute rejection per patient were significantly lower in the ECP arm after 6 months (Barr, 1998). 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 study found decreased number of rejection episodes in 6 months after ECP compared to 6 months before initiation of therapy (1.5 vs. 0.5, $P = .002$; Carlo, 2014).

The goal of TPE is to remove donor-specific antibodies and/or inflammatory mediators, while complimentary medications suppress clinically significant DSA production. Not all antibody levels can be significantly reduced by TPE and inclusion of TPE in desensitization and AMR prophylaxis regimen is often limited to those whose DSA mean fluorescence intensity (MFI) show a sufficient decrease in 1:16 sera dilution studies (Mazzei 2021). Neither ECP nor TPE is recommended as a monotherapy in desensitization, rejection prophylaxis, or AMR. Studies utilizing TPE for desensitization, AMR prophylaxis, and AMR treatment have been largely observational and retrospective. The identification of pathogenic DSA typically includes Luminex-based single antigen bead analysis supported by titer, complement (e.g., C1q or C4d), or IgG subclass studies. Clinically actionable antibody thresholds for desensitization, AMR prophylaxis, or AMR treatment remain unstandardized and programmatically defined. Desensitization therapies are often reserved for patients with pre-transplant panel reactive antibody (PRA) levels of >50% and may utilize TPE, IVIG, bortezomib, and/or rituximab (Colvin, 2019). In a 70 patient retrospective review at a pediatric center, 14 had high PRA and 56 did not (Asante-Korang, 2015). PRA levels were significantly decreased following desensitization protocol including TPE, IVIG, cyclophosphamide, and rituximab. Overall mortality and rejection episodes were decreased in the high PRA group, presumably due to this aggressive desensitization approach.

Technical notes

Volume treated: ECP: varies; TPE: 1 to 1.5 TPV

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

Frequency: ECP: one cycle weekly, tapered over several months; TPE: Daily or every other day

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Duration and discontinuation/number of procedures

In most centers, an ECP series consists of 2 procedures (1 cycle) performed weekly and eventually tapered. For refractory or recurrent rejection, ECP cycles have been performed weekly to every six weeks over a 6 to 18 month treatment period (Slomovich, 2021). A commonly employed prophylactic AMR approach is five cycles in first month post-transplant followed by one cycle every other week in the second and third months post-transplant, followed by monthly cycles for the fourth, fifth, and sixth months post-transplant (Barr, 1998; Slomovich, 2021). There are no clear criteria for discontinuing ECP treatment, but they are typically continued until DSA are cleared to clinically inactionable levels or improvement/stabilization of symptoms are seen. Regarding TPE, improvement in heart function, biopsy findings, and DSA levels are often used to determine timing of discontinuation. For desensitization or AMR prophylaxis, a commonly published approach is 1 to 3 pre-transplant TPE with IVIG, followed by 3 to 5 post-transplant TPE with IS. For treatment of AMR, TPE are generally performed daily or every other day for a week, with treatments extended or tapered as needed for clinical response. Given concerns for peri-procedural bleeding in the immediate post-transplant period, supplemental use of plasma as a replacement fluid may be considered.

Keywords: heart/cardiac transplantation, cellular rejection, humoral rejection, antibody mediated rejection, transplant vasculopathy, photopheresis, plasma exchange, desensitization

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TRANSPLANTATION, HEMATOPOIETIC STEM CELL, ABO INCOMPATIBLE

Incidence: ABOi in 20% to 50% of allogeneic HSCT; PRCA in 8% to 26% of major ABO incompatible

Indication	**Procedure**		**Category**	**Grade**
Major ABOi, HPC(M)	TPE		II	1B
Major ABOi, HPC(A)	TPE		II	2B
Minor ABOi, HPC(A)	RBC exchange		III	2C
Pure red cell aplasia	TPE		III	2C
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Major ABOi	0	0	6 (520)	NA
Minor ABOi	0	0	3 (40)	0
Pure red cell aplasia	0	0	2 (7)	23 (31)

ABOi = ABO incompatible; HSCT = hematopoietic stem cell transplant; PRCA = pure red cell aplasia; HPC(M) = hematopoietic progenitor cell, marrow; HPC(A) = hematopoietic progenitor cell, apheresis.

Description

The human leukocyte antigen (HLA) and blood group antigens are inherited independently; as such, approximately half of all allo-hematopoietic stem cell transplants (HSCTs) are performed across the ABO blood group barrier. Three distinct types of ABO incompatibility (ABOi) are described: major, minor, and bidirectional (i.e., both major and minor incompatibility present). Major ABO incompatible refers to the presence of natural antibodies (isohemagglutinins) in the recipient against donor A and/or B blood group antigens, that may cause acute hemolysis of the red blood cells (RBCs) present in infused hematopoietic progenitor cell (HPC) products. HPC products collected by apheresis, HPC(A), contain a small volume of RBCs (2%-5% hematocrit), typically measuring <20 mL; therefore, acute hemolysis is uncommon and does not generally require intervention. By comparison, bone marrow HPC products, HPC(M), contain 25% to 35% RBCs by volume, leading to a higher risk of acute, clinically significant hemolysis. Cord blood HPC products typically contain insufficient amounts of intact RBCs to induce hemolysis. After major ABO incompatible transplant, RBC engraftment may be delayed in up to 20% to 30% of cases, and 8% to 26% of patients develop pure red cell aplasia (PRCA) due to persistence of isohemagglutinins that destroy donor erythroid precursors. Pre-transplant isohemagglutinin titers are not always predictive of delayed engraftment or PRCA after major ABO-incompatible transplant.

Minor ABO incompatible refers to the presence of isohemagglutinins in the plasma of the donor HPC product against the recipient A and/or B antigens. 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 to 10 days post-transplant and is caused by donor B lymphocytes that mount an allo-antibody response against host A or B antigens.

Current management/treatment

In major ABO incompatibility, acute hemolysis can be avoided by removing RBCs from the HPC product through automated RBC depletion, or by reducing recipient isohemagglutinin titers. RBC depletion, which may incur loss of HPCs, is based on institutional guidelines, which usually limit the total infusion of fresh donor RBCs to 10-40 mL. Recipient isohemagglutinin reduction is performed largely by TPE. IA is also available in some countries. In some European centers, isohemagglutinin titer reduction may be accomplished by slowly infusing donor-type RBCs to adsorb antibodies in vivo. Selective ABO immunoadsorption has also been reported, though without clear differences in clinical outcomes (Crysandt, 2021). Post-transplant PRCA in the setting of major ABO incompatibility usually recovers with early withdrawal of immunosuppression (cyclosporine) and supportive transfusion. Persistent cases may respond to exogenous erythropoietin, rituximab, donor lymphocyte infusions, eltrombopag (Busca, 2018), and/or TPE.

In minor ABO incompatible transplants with donor isoagglutinin titer >128 and HPC plasma volume >200 mL, product plasma reduction is performed to prevent acute recipient hemolysis. However, plasma reduction does not reduce the B lymphocyte content nor the incidence of PLS. PLS is unpredictable and managed expectantly with aggressive transfusions. Pre-transplant RBC exchange using group-O RBCs to reduce the volume of donor-antibody incompatible RBCs has been reported, with reduced severe hemolysis and transplant-related mortality compared to historical controls (Worel, 2007). A separate single-center study of day +4 RBC exchange failed to show significant improved outcomes for select patients at higher risk of hemolysis (Cunard, 2014). PLS has been anecdotally treated with TPE to rapidly reduce isoagglutinin titer.

Rationale for therapeutic apheresis

For major ABO incompatible transplants, TPE is performed to reduce the recipient isohemagglutinin titer prior to HPA-(A) product infusion and can be used as an alternative to RBC depletion of the product. TPE may also improve post-transplant PRCA by removing persistent recipient isohemagglutinins. ABO-specific immunoadsorption columns have also been used successfully in a small CS (Handisurya, 2020).

For minor ABO incompatible transplants, 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 recipient RBC population ≤35% can significantly mitigate delayed hemolysis in high-risk patients. Smaller studies, however, have not demonstrated clear benefit of RBC exchange in reducing hemolysis when performed following infusion of the HPC product.

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Technical notes

TPE should be performed before infusion of major ABO incompatible HPC product, using albumin or a combination of albumin and plasma compatible with both donor and recipient as replacement fluid. Automated RBC exchange replaces 1 to 1.5 patient's RBC volume with group O RBCs. RBC exchange to 35% residual recipient RBCs.

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

Keywords: ABO incompatible, passenger lymphocyte syndrome, hematopoietic stem cell transplantation, hematopoietic progenitor cell, pure red cell aplasia, plasma exchange, red blood cell exchange

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TRANSPLANTATION, HEMATOPOIETIC STEM CELL, HLA DESENSITIZATION

Incidence: DSA in 3% to 24% of allogeneic hematopoietic stem cell transplantation recipients

Procedure	**Category**		**Grade**	
TPE	III		2C	
# reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
	0	0	7 (96)	11 (16)

DSA = donor-specific antibody directed against human leukocyte antigen (HLA) antigens.

Description

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative treatment for both malignant and non-malignant disorders. A significant number of patients lack an HLA-identical sibling donor, therefore, alternative sources of stem cells, including matched-related or unrelated, mismatched unrelated, haploidentical, or umbilical cord can be used. Many transplant candidates will have pre-formed donor specific antibody (DSA) directed against the donor's class I and/or class II HLA antigens; the published literature reports an incidence rate of 3% to 24% and are more common in adult than pediatric allo-HSCT recipients. Common allosensitization exposures include blood product transfusion, pregnancy, and prior organ or allo-HSCT transplantation. It is important to note that methods of testing for HLA DSA vary by laboratory. Clinical studies suggest that the presence of HLA DSA significantly increases the risk of primary engraftment failure.

Current management/treatment

Current strategies are aimed at identifying and defining HLA antibodies present in the recipient once the donor search has been performed and, if possible, to use this information to avoid selection of allogeneic donors with cognate antigens. The DSA mean fluorescence intensity (MFI) considered positive and necessitating intervention varies among studies. If the donor availability is limited, potential approaches to address elevated HLA DSA include the use of TPE, IA, IVIG, rituximab, and bortezomib. The number of reports with the use of TPE/IA is limited. The largest study included 14 patients, and utilized a protocol including tacrolimus, mycophenolate mofetil, TPE and IVIG, modeled on desensitization protocols commonly used for incompatible kidney transplant desensitization (Leffell, 2015). CRs of pre-transplant buffy coat or platelet transfusions from the HSCT donor (expressing DSA-cognate HLA Class I antigens) have been published (Ciurea, 2015; Bailén, 2021); such infusions have successfully decreased DSA levels and resulted in donor stem cell engraftment.

Rationale for therapeutic apheresis

Due to the now recognized role of DSA in engraftment failure, elimination/reduction of these antibodies peri-transplant may result in improved outcomes. Experience with TPE alone for desensitization is limited, with associated concerns of DSA titer rebound without use of concomitant immune suppression (Choe, 2019). The limited CRs and CS of HLA desensitization (primarily using TPE and another modality) suggest that after adequate desensitization, engraftment successfully occurs in most 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 one CS of HSCT candidates with HLA DSA, the desensitization protocol included alternate-day, single-volume TPE followed by low dose (100 mg/kg) CMV hyper-immmune IVIG (Leffell, 2015). Treatment also included tacrolimus and mycophenolate mofetil during desensitization, and bortezomib ~3.5 months prior. Using this protocol, DSA levels were decreased in all patients (mean reduction of 64%). Thirteen of the 14 patients' DSA were below levels typically associated with positive flow cytometric crossmatches; all underwent HSCT and engrafted successfully by day +60. Although it is unclear if 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.

In a cohort of 37 patients who are HLA DSA-positive receiving haploidentical HSCT, multimodal treatment consisting of alternate-day TPE, rituximab, IVIG, and HLA-matched buffy coat infusions were given. This group was compared to 345 DSA-negative historical controls. Outcomes including graft and overall survival were similar between patients who are DSA-positive and controls with the exception of those presenting with initial DSA >20,000 MFI and those with persistent C1q positivity after desensitization; as an example, the sub-distribution hazard ratios for overall survival were 4.09 and 5.82, respectively (Ciurea, 2021). In a pediatric case series, 43 patients with HLA antibodies (>1000 MFI) were compared to 42 patients without HLA-antibodies matched for age, sex, donor type, and underlying disease. Donor specificity of HLA antibodies was not considered. Thirty-eight patients who were HLA antibody positive received a form of desensitization, 12 of these treatments included TPE: (2) TPE alone, (7) TPE + corticosteroid, and (3) TPE, corticosteroid, and rituximab. Engraftment and survival were similar between the two groups, though the impact of desensitization on these outcomes was not evaluated (Akinci, 2022). Additional, larger controlled studies are warranted to fully establish the overall impact of these desensitization regimens, and specifically the role of TPE, on engraftment in DSA-positive allogeneic HSCTs.

Technical notes

Volume treated: 1 TPV

Frequency: Every other day

Replacement fluid: Albumin

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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 one CS, TPE was not performed during pre-transplant conditioning or with post-transplant cyclophosphamide but implemented before conditioning with one additional treatment on the day before graft infusion (Gladstone, 2013). Flow crossmatch positive patients received 4 to 5 treatments and complement-dependent cytotoxic crossmatch positive patients received additional treatments. In addition, patients with DSA rebound may require additional TPE treatments in the post-transplant phase.

Keywords: hematopoietic stem cell transplantation, desensitization, hematopoietic progenitor cell, graft rejection, plasma exchange

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TRANSPLANTATION, INTESTINE

Incidence: rejection ~45% w/in 1 year post-transplant, mostly cellular; DSA contributes to acute/chronic rejection

Indication	Procedure	Category	Grade
Antibody mediated rejection	TPE	III	2C
Desensitization			

# reported patients: <100	RCT	CT	CS	CR
Antibody mediated rejection	0	0	5 (29)	3 (3)
Desensitization	0	0	2 (9)	2 (3)

DSA = donor-specific antibody directed against human leukocyte antigen (HLA) antigens.

Description

Since the first human small bowel transplant in 1967, intestinal transplantation (ITx) has evolved as an indicated therapy for patients with short bowel syndrome due to congenital anomalies or necrotizing enterocolitis in children; Crohn's disease, mesenteric thrombosis, or trauma in adults; or severe complications attributed to chronic parenteral nutrition. It can be performed as an isolated ITx or in combination with other organs in a multivisceral transplant. Compared to other solid organ transplants, ITx is less frequent (~3,286 transplants between 1990 and 2021 based on data from the Organ Procurement and Transplantation Network). The small intestine is a lymphoid organ and thus, can be significantly immunogenic. Due to advancement in immunosuppression, patient and graft survival, as well as quality of life, have improved significantly in recent years. Complications of ITx include: infections (leading cause of death), rejection, solid-organ associated acute graft versus host disease, and post-transplant lymphoproliferative disorder.

Rejection can be acute (humoral and/or cellular) or chronic; acute rejection in patients with ITx is likely caused by a combination of both antibody-mediated and T-cell mediated processes. Acute rejection can be evidenced through laboratory parameters (donor specific HLA antibody [DSA] levels, fecal calprotectin level [higher in rejection compared to other causes of enteritis], and serum citrulline [inversely proportional to the severity of acute rejection]), histologically (C4d positivity, mononuclear infiltrate, crypt injury and apoptosis), and/or clinical graft dysfunction (increased stoma output, fever, abdominal pain, and ileus). Historically, ITx acute rejection was attributed to T-cell activity; however, antibody mediated rejection (AMR) may play an important role in rejection and graft loss. Similar to other organ transplants, both preformed and de novo DSA play an important role in both acute and chronic ITx graft rejection as well as survival.

Current management/treatment

Treatment for mild rejection includes corticosteroids and, in steroid resistant cases, thymoglobulin. Along with TPE, other treatments for AMR can include IVIG, rituximab, bortezomib, vedolizumab, and eculizumab.

Similar to the treatment of AMR, TPE along with other immunosuppressive medications, such as IVIG, rituximab, and/or bortezomib can be used in desensitization protocols (Gondolesi, 2006; Cheng, 2017; Santeusanio, 2019); however, the optimal desensitization protocol for sensitized patients is not known. Approaches tend to be center-specific and are tailored to the severity of the patient's illness.

Rationale for therapeutic apheresis

Treatment of AMR requires a multifaceted approach, including suppression of antibody production, removal of antibody, and inhibition of complement activation. TPE can remove existing alloantibodies, such as de novo DSA, but it needs to be used in conjunction with other immunosuppressive therapies to prevent their formation. Support for using TPE in the treatment of AMR is primarily restricted to CRs and small CS. One study detailed use of TPE (5-11 treatments) in 6 patients with ITx (3 adults and 3 children) with elevated DSA (>1000 mean fluorescence intensity (MFI) as cut-off). All demonstrated reduced DSA levels and histological resolution of rejection after TPE; only one patient with symptomatic rejection did not have symptom resolution after treatment (Bobr, 2020). Another described an institutional experience using TPE (3-5 procedures) in pediatric patients with ITx with elevated DSA (>1000 MFI as cut-off) in combination with other immunosuppressive therapies. Ten of ten patients with elevated DSA without clinical symptoms were weaned from parenteral nutrition, 5 of which received TPE treatment. In the 9 patients with elevated DSA and evidence of clinical rejection, 7 received TPE treatment of which 4 showed clinical improvement (Petit, 2017). One study described their institutional protocol for ITx rejection treatment in adults, including TPE (5 procedures every other day) with alternating IVIG (10 g/day) when DSA is detected (no fixed MFI-based cut-off), rituximab (in the setting of DSA persistence), and bortezomib (for treatment refractory AMR); of 10 symptomatic patients with elevated DSA, 9 recovered from AMR (Gerlach, 2014). Similar rationale applies to the use of TPE in desensitization, with the goal of reducing preformed DSA to avoid antibody-mediated allograft injury. Patients with high levels of DSA post-transplant (despite desensitization) often require additional immunosuppression, including TPE treatment.

Technical notes

Volume treated: 1 to 1.5 TPV

Frequency: Daily or every other day

Replacement fluid: Albumin, plasma

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Duration and discontinuation/number of procedures

For treatment of rejection, approximately 5 to 7 TPE procedures have been reported. Improvement in DSA levels, biopsy findings, and/or clinical symptoms can be used to determine the timing of discontinuation. For desensitization purposes, varied goals were used in published protocols, including reduction of calculated panel reactive antibody (cPRA) to <20% to 30% of baseline or negative flow crossmatch. Prophylactic posttransplant TPE treatment may be considered and usually is determined by risks of AMR and/or pre-transplant DSA levels. Despite prior desensitization treatment, measurement of post-transplant DSA levels should assist in the diagnosis of AMR, and the timing and type of immunosuppressive therapies to utilize (including TPE), if indicated.

Keywords: desensitization, antibody mediated rejection, donor specific antibody, plasma exchange, small bowel transplant, intestinal transplant

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TRANSPLANTATION, KIDNEY, ABO COMPATIBLE

Incidence: AMR ~10%, ~40% with desensitization; HLA sensitization ~30%

Indication	Procedure		Category	Grade
Antibody-mediated rejection	TPE/IA		I	1B
Desensitization/prophylaxis, living donor				
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Antibody-mediated rejection	3 (61)	11 (507)	NA	NA
Desensitization/prophylaxis, living donor	0	6 (583)	NA	NA

AMR = antibody-mediated rejection; HLA = human leukocyte antigen; LD = living donor.

Description

The use of traditionally immunologically incompatible kidneys has expanded access to kidney transplantation despite conventional donor organ shortages and increased sensitization among prospective recipients. Human leukocyte antigen (HLA) antibodies result from exposure to foreign HLAs during transfusions, pregnancy, or transplantation. Sensitization presents a barrier to transplantation, as patients with numerous HLA antibodies and a corresponding high calculated panel reactive antibody (cPRA) score have difficulty finding HLA compatible donors and remain on the transplantation list significantly longer than unsensitized patients. HLA antibodies when complimentary to a donor HLA antigen type are termed donor specific antibodies (DSA).

Antibody mediated rejection (AMR), secondary to HLA DSA or non-HLA antibodies, is a leading cause of early and late allograft injury. Diagnosis of AMR is based on the 2019 Banff classification and relies on (1) histologic evidence of acute tissue injury; (2) evidence of current or recent antibody interaction with vascular endothelium; and (3) serologic evidence of circulating DSA (to HLA or other antigens). Recipients at higher risk include those with previous transplants and high cPRA. Subclinical AMR leads to chronic humoral rejection and late graft loss.

Transplanting a kidney into a recipient with strong pre-existing DSA is associated with AMR and poor allograft outcomes. In addition, increased levels of non-HLA antibodies (e.g., AT1R, MICA, ETAR, agrin, myosin, perlecan, vimentin and tubulin antibodies) have also been associated with allograft rejection risk, though pre-transplant AT1R antibodies have been the most extensively studied. The lack of standardized and clinically relevant cut-offs for non-HLA antibody evaluation remains a limitation of this research.

Current management/treatment

To prevent acute kidney allograft rejection, patients are generally treated with antithymocyte globulin (ATG) induction and maintenance tacrolimus and mycophenolate mofetil, with or without prednisone. There are a number of AMR treatment options, including methylprednisone, ATG, TPE, IVIG, rituximab, imlifidase, ATG, cyclophosphamide, IL-6 inhibitors, bortezomib, and eculizumab. Few RCTs exist to compare these regimens, though TPE and IVIG with or without rituximab remain the most commonly used. Clinical trials have demonstrated improved graft survival with TPE + IVIG versus either alone, or TPE + rituximab versus TPE alone. A non-randomized study compared high-dose IVIG with TPE + IVIG + rituximab and showed both better graft survival and lower DSA levels post-transplant with the latter (Lefaucheur, 2009). However, use of rituximab has been associated with increased rates of infection.

Desensitization/prophylaxis regimens typically include IVIG, TPE/ IA, rituximab, ± additional immunosuppression, aimed at reducing antibody levels to a predetermined mean fluorescence intensity (MFI) cut-off or converting a positive flow crossmatch result to negative prior to transplant. For patients with elevated pre-transplant AT1R levels, desensitization/prophylaxis strategies have utilized angiotensin receptor blockade (ARB) medication with adjunctive perioperative TPE to achieve comparable rates of rejection and graft survival when compared to patients with lower preoperative AT1R levels (Carroll, 2019). TPE-based desensitization regimens have been shown effective for those awaiting living donor transplants or within the context of kidney paired donations "kidney swaps." A multicenter study demonstrated higher survival rate at 1-, 3-, 5-, and 8-years post-transplant in recipients from incompatible donors when compared to patients who either did not undergo transplant or those who waited for transplant from deceased donor (Montgomery, 2011). Given the transient effect of desensitization (if effective), unpredictable timing of deceased donor organ offers, and the rapid allocation process, TPE-based desensitization protocols are poorly applicable to candidates awaiting deceased donor kidneys.

Rationale for therapeutic apheresis

In AMR, DSA and non-HLA antibodies can be removed with TPE, DFPP, and IA. Apheresis is always performed in conjunction with other immunosuppressive drugs. CS 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. Current regimens that include TPE have graft survival rates of 70% to 80% (90% in reports with TPE, IVIG, and rituximab).

Perioperative TPE/IA, in combination with immunosuppressive drugs, can be used to reduce HLA and non-HLA antibody levels to an acceptable clinical threshold (predetermined antibody level or flow crossmatch negative). TPE is performed both prior to and after

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transplant, and re-initiated if AMR occurs. Desensitization protocols are appropriate in carefully selected patients, as not all antibodies can be effectively diminished.

Technical notes

Both TPE and IA demonstrate significant impacts on fibrinogen levels. Use of plasma as a partial or full replacement fluid should be considered in the perioperative period.

Volume treated: 1 to 1.5 TPV **Frequency:** Daily or every other day

Replacement fluid: Albumin, plasma

Duration and discontinuation/number of procedures

For AMR, protocols may use 5 or 6 TPE daily or every other day or may base the number of treatments on post-TPE kidney function improvement and decreasing DSA or non-HLA antibody levels.

For desensitization/prophylaxis protocols, pre-operative TPE is typically performed daily or every other day for 1 to 5 sessions until flow crossmatch becomes negative. TPE is then continued postoperatively for a minimum of 3 procedures. Further treatment is determined by risk of AMR, DSA titers, or the occurrence of AMR.

Keywords: kidney/renal transplant, ABO compatible, transplant rejection, desensitization, plasma exchange, immunoadsorption

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TRANSPLANTATION, KIDNEY, ABO INCOMPATIBLE

Incidence: rare

Indication	Procedure		Category	Grade
Desensitization, living donor	TPE/IA		I	1B
Antibody mediated rejection	TPE/IA		II	1B
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	0	13 (4814)	NA	NA

Description

Due to a relative shortage of compatible organs for kidney transplantation, ABO incompatible (ABOi) living donors are used. As of July 27, 2022, 89,874 US candidates are on the United Network for Organ Sharing (UNOS) kidney transplant waiting list to receive an allograft. In 2021 (United States), 24,670 kidney transplants were performed with 24% of these utilizing living donors. Major incompatibility refers to the presence of natural antibodies (isoagglutinins) in a recipient's blood against a donor's A or/and B blood group antigen(s). Major ABOi exists in ~35% of random donor-recipient pairs. A, B, and AB donor organs have been successfully transplanted into ABOi recipients with desensitization strategies. Without desensitization, these antibodies can cause severe antibody mediated rejection and hyperacute rejection resulting in allograft loss. An optimal desensitization regimen allows for accommodation, or preservation of long term graft function and histology despite circulating isoagglutinins, while balancing immunosuppression-related risks of infection. Post-operative elevated anti-A, B, or A,B (A/B) antibodies with accompanying graft dysfunction, typically within the first month, may require additional treatment for antibody mediated rejection (AMR). Treatment for AMR due to human leukocyte antigen (HLA) antibodies is described elsewhere (see Transplantation, kidney, ABO compatible). Coexistent ABO and HLA incompatible kidney transplant recipients demonstrate higher risks of AMR than solely ABO or HLA incompatible cohorts (Ko, 2017; Pandey, 2021).

Current management/treatment

Protocols vary, but desensitization for ABOi kidney transplants typically involves some combination of pretransplant B cell depletion with rituximab, removal of anti-A or anti-B isoagglutinins via apheresis (TPE, IA, or DFPP), IVIG, and varied peri-transplant immunosuppressive medications (e.g., tacrolimus, mycophenolate mofetil, prednisone, anti-thymocyte globulin [ATG] cyclosporine, basiliximab, daclizumab, everolimus, bortezomib and eculizumab). Apheresis approaches should be tailored to the pre-treatment and post-treatment goal anti-A/B titers. ABOi kidney transplantation may also be 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 group O recipients, but KPD is not available in all countries. ABOi kidney transplants are associated with increased risk of post-transplant sepsis compared to ABO compatible transplants, but risks of urinary tract infections, cytomegalovirus infection, BK polyomavirus infection, and *Pneumocystis jirovecii* pneumonia may not be different (Scurt, 2019). More recent publications demonstrate comparable outcomes of ABOi and ABO compatible kidney transplants and may be a result of improved desensitization strategies.

The A2 blood subgroup has reduced expression of the A antigen on RBCs and endothelium, which can be exploited in transplantation. A2 donors are preferred over group A1 donors in group O or B recipients in living donor ABOi kidney transplantation as they have a lower risk of graft rejection. UNOS permits A2/A2B deceased donor kidney transplantation into group O or 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

Isoagglutinin tiers at the time of transplant are associated with risk of early antibody mediated rejection and apheresis can reduce anti-A and/or anti-B levels. Optimal post-desensitization anti-A/B antibody levels have not been defined, but generally range between 1:8 and 1:32. Both short and long-term ABOi kidney transplant survival statistics compare well with that seen in ABO-compatible transplants. TPE, DFPP, and ABO-antigen specific and non-specific IA columns have been used to remove ABO antibodies.

Technical notes

The replacement fluid for TPE is albumin and/or plasma (compatible with both the recipient and donor ABO type), depending upon presence of coagulopathy and temporal proximity to surgical intervention. In the immediate pre- and post-surgical setting, full or partial replacement with plasma is typically used as a higher incidence of early bleeding complications has been shown among ABOi versus ABO compatible kidney transplants and is attributed to perioperative TPE treatments (Scurt, 2019). Close monitoring of coagulation status is recommended. Antibody removal by IA is also efficacious and allows for preservation of clotting factors while obviating the need for blood product derived replacement fluids.

Volume treated: 1 to 1.5 TPV for TPE; 1.5 to 2.5 TPV for IA

Frequency: Daily or every other day

Replacement fluid: Albumin, plasma

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Duration and discontinuation/number of procedures

The duration of treatment should be guided to achieve a pre-defined critical anti-A/B IgG threshold prior to transplant, taking antibody production and rebound phenomenon into account. Of note, titer results may vary by institution given differing titration methods and reagents. Most anti-A/B AMR episodes occur within the first 2 weeks following transplantation. Post-transplant ABO titers are not correlated with the incidence of rejection. Additionally, C4d positivity is very common in transplanted ABOi kidney biopsies and is not a useful marker for rejection in the absence of light microscopic changes suggestive of rejection.

Keywords: ABO incompatible, kidney/renal transplantation, desensitization, rejection, plasma exchange

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TRANSPLANTATION, LIVER

Incidence: rare					
Indication	**Procedure**	**Category**		**Grade**	
Desensitization, ABOi LDLT	TPE	I		1C	
Desensitization, ABOi DDLT*/AMR**	TPE	III		2C	
AMR/Immune suppression withdrawal	ECP	III		2B	
Desensitization, ABOi	ECP	III		2C	
# reported patients: >300	**Procedure**	**RCT**	**CT**	**CS**	**CR**
Desensitization, ABOi LDLT	TPE	0	0	>10 (>200)	NA
Desensitization, ABOi DDLT/AMR	TPE	0	0	12 (116)	NA
AMR/Immune suppression withdrawal	ECP	0	3 (457)	NA	NA
Desensitization: ABOi	ECP	0	2 (31)	0	0

ABOi = ABO-incompatible; LDLT = living donor liver transplant; DDLT = deceased donor liver transplant; AMR = antibody mediated rejection; *TPE based desensitization is not indicated in the setting of group A-subtype (e.g., A_2) into group O DDLT; **includes ABOi and donor-specific antibody (DSA) directed against human leukocyte antigen (HLA).

Description

Liver transplantation can be a life-saving procedure. Due to a relative shortage of compatible organs for transplantation and the development of more effective immune modulation protocols, ABO-incompatible (ABOi) liver transplants are frequently being performed, from both living (segmental) and deceased donors. ABO isoagglutinins may cause hyperacute/acute humoral rejection due to direct, antibody-induced endothelial damage (A and B antigens are expressed on vascular endothelium). Many publications, including an expert panel report on the impact of donor specific human leukocyte antigen (HLA) antibodies on short- and long-term outcomes in liver transplantation, suggest an additional role of anti-HLA antibodies in mediating liver allograft injury (O'Leary, 2014).

Current management/treatment

In the ABOi deceased donor liver transplant (DDLT) setting, TPE is typically instituted immediately prior to or both prior to and following transplantation to prevent hyperacute/acute antibody mediated rejection (AMR) in patients with high anti-A and anti-B isoagglutinin titers. With the introduction of rituximab (as part of desensitization protocols which often include TPE, IVIG, corticosteroids, with or without local hepatic infusion of prostaglandin E1), ABOi living donor liver transplant (LDLT) has been increasingly utilized with very good 1-, 3-, and 5-year survival statistics. As in the ABOi kidney transplant setting, rituximab appears to be as effective as splenectomy in enabling ABOi LDLT. Two retrospective studies in 46 and 40 adults, respectively, undergoing ABOi LDLT received rituximab with or without TPE for desensitization (Lee, 2015; Yamamoto, 2018). In both, there were no differences in survival, rebound anti-blood type isoagglutinin titers, or other potential complications, suggesting that rituximab may be sufficient for desensitization. Individuals with the A_2 blood group have reduced expression of the A antigen on endothelium and RBCs; a large retrospective CS of patients undergoing DDLT suggests A_2 into O transplants are safe with similar graft and overall survival relative to ABO-compatible DDLT and additional therapy is not necessary (Kluger, 2012). Multiple studies suggest that several liver pathologic conditions including hyperacute rejection, "steroid-resistant" rejection, idiopathic/accelerated fibrosis and biliary strictures, have been associated with human leukocyte antigen (HLA) donor-specific antibodies (O'Leary, 2014).

Rationale for therapeutic apheresis

Apheresis modalities including TPE and ECP can be utilized to desensitize in the setting of ABO incompatible (ABOi) transplantation, prevent/treat biopsy proven rejection, and substitute for traditional immune suppression. There are no controlled clinical trials using TPE in ABOi liver transplantation. However, given the significant risks of hyperacute/acute AMR, TPE continues to be used as a key therapeutic modality to reduce anti-A or anti-B isoagglutinin titers in the peri-transplant period. In ABOi LDLT, TPE is extensively used as part of a desensitization protocol to lower antibody titer(s) below a critical threshold (which differs institutionally based on titration method/technique) prior to the transplant procedure. Basiliximab, IVIG, and other agents are sometimes used pre- and/or post-transplant (Kim, 2018; Lee, 2021). In ABOi 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 liver transplant allograft AMR to decrease levels of HLA donor-specific antibodies and anti-A or anti-B isoagglutinins. Several 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 have been proposed and appear to identify liver transplant recipients at highest risk for allograft loss (O'Leary, 2016). For chronic AMR, TPE is used in conjunction with rituximab, IVIG, bortezomib, other monoclonal antibodies, and standard immunosuppressive medications such as steroids, a calcineurin inhibitor, and mycophenolate mofetil (Tajima, 2019; Komagone, 2022).

ECP has been utilized in several clinical scenarios in patients following liver transplantation (Mazzoni, 2017). It has been prescribed early in the post-transplant period as prophylaxis against rejection in patients with high risk for calcineurin inhibitor (CNI) induced toxicity, allowing later introduction of traditional immunosuppression. It has also been used in the setting of ABOi liver transplantation with the goal of preventing AMR. Finally, ECP has been used to reduce immune suppression in patients with hepatitis C and biopsy proven acute rejection, along with anti-viral therapy. Treatment schedules for ECP vary among studies.

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Technical notes

The replacement fluid for TPE is albumin, plasma, or a combination of both (plasma should be compatible with both the recipient and donor organ ABO type in ABOi transplants). If an underlying coagulopathy secondary to liver failure is present, plasma may be helpful in assisting to transiently correct this abnormality. Typical anticoagulation used is anticoagulant citrate dextrose, solution A (ACD-A); heparin-based anticoagulation may be considered if liver function is poor.

Volume treated: TPE: 1-1.5 TPV; ECP: varies

Frequency: TPE: daily or every other day. ECP: one cycle weekly or every 2-8 weeks for several months

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

Duration and discontinuation/number of procedures

The goal of therapy in the setting of ABOi is to reduce the ABO isoagglutinin titer to less than a critical threshold prior to transplant; the threshold of critical titer is center specific. The number of TPE procedures required depends upon the patient's baseline isoagglutinin titer and on the rate of antibody production/rebound following TPE. For ECP, the duration of therapy varies among studies. Patients should be monitored closely for graft dysfunction before discontinuation of TPE or ECP. For treatment of liver rejection, TPE and ECP are usually used until improvement in liver function (such as liver enzymes, bilirubin, etc.) is achieved.

Keywords: ABO-incompatible liver transplantation, deceased donor liver transplant, living donor liver transplant, liver rejection, liver humoral rejection, antibody mediated rejection, immune suppression withdrawal, plasma exchange, extracorporeal photopheresis

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TRANSPLANTATION, LUNG

Incidence: BOS: ~25% at 3 years, 50% at 5 years; acute AMR: ~4%; hyperacute AMR: rare

Indication	Procedure	Category	Grade
Chronic lung allograft dysfunction Bronchiolitis obliterans syndrome	ECP	II	1C
Antibody mediated rejection Desensitization	TPE	III	2C

# reported patients: >300	RCT	CT	CS	CR
Chronic lung allograft dysfunction/ Bronchiolitis obliterans syndrome	0	0	>10 (>200)	NA
Antibody medicated rejection	0	0	8 (159)	NA
Desensitization	0	0	2 (543)	NA

BOS = bronchiolitis obliterans syndrome; AMR = antibody mediated rejection.

Description

Chronic lung allograft dysfunction (CLAD) includes multiple disorders, the most common being bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS). Recurrent acute cellular rejection (ACR) increases the risk of developing BOS; approximately half of lung transplant recipients develop BOS within 5 years. BOS, an obstructive ventilating defect affecting the small airways, can be difficult to diagnose by transbronchial biopsy; diagnosis is typically made based on graft deterioration as assessed by pulmonary function testing (PFT). It is defined by a significant (>20%) and sustained (>3 weeks) decline in expiratory flow rates, provided that alternative causes are excluded. The most precipitous decline in airflow typically occurs in the first 6 months following a diagnosis of BOS, although time of onset and rate of FEV_1 decline are highly variable. Single lung transplantation conveys a higher risk for earlier onset of BOS compared with bilateral, and unfavorable outcomes are associated with rapid onset and pre-transplant idiopathic pulmonary fibrosis. The International Society for Heart and Lung Transplantation (ISHLT) defined and proposed diagnostic criteria for antibody mediated rejection (AMR) of the lung, including both symptomatic and preclinical forms (Levine, 2016). Development of AMR is associated with increased morbidity, CLAD, and subsequent graft failure. Lung transplant is often avoided in the setting of pre-formed donor-specific anti-human leukocyte antigen (HLA) antibodies because of the risk of hyperacute rejection and AMR.

Current management/treatment

At the time of transplantation, many centers employ an induction regimen targeting host lymphocytes, using agents such as antithymocyte globulin (ATG), or monoclonal agents against surface CD3 (OKT3), IL-2 receptor/CD25 (daclizumab, basiliximab) or CD52 (alemtuzumab). Maintenance immunosuppression post-transplant typically consists of a 3-drug regimen that includes a calcineurin inhibitor (cyclosporine or tacrolimus), antimetabolite (azathioprine or mycophenolate mofetil), and corticosteroids. Short courses of intravenously pulsed corticosteroids followed by a temporary increase in maintenance doses for a few weeks are the preferred treatment for uncomplicated acute rejection. The initial treatment of BOS usually consists of repeated pulses of high-dose methylprednisolone. For patients with unresponsive BOS, salvage therapies have included methotrexate, ATG, or muromonab-CD3. Azithromycin, an effective immunomodulator, has shown efficacy in improving forced expiratory volume (FEV_1) and is frequently prescribed as an adjunctive therapy. A small retrospective CS comparing alemtuzumab to ECP in adult patients with CLAD showed significant improvement in FEV_1 but no difference between the two groups (Moniodis, 2018). Another study reported on 12 adult patients in whom ECP therapy was terminated due to cessation of country-wide insurance coverage; within a year, 7 died and the survivors had significant decline in lung function (Robinson, 2017). Treatment protocols for lung AMR are primarily adapted from evidence treating AMR in other allografts (e.g., kidney, heart), with no RCTs or direct comparisons currently available. Therapies include pulsed corticosteroids, IVIG, TPE, rituximab, and proteosome inhibitors (e.g., bortezomib, carfilzomib).

Rationale for therapeutic apheresis

Initially, ECP was used in the context of severe, refractory BOS, with efficacy demonstrated by FEV_1 stabilization or improvement. ECP may also be effective for stabilization of lung function in patients with persistent acute rejection and early, less severe BOS, potentially preventing further loss of pulmonary function. There have also been CS reporting lower rates of BOS in patients with ACR treated with ECP, suggesting a preventative role. Both anti-HLA and "lung-associated self-antigens" (SAgs, e.g., tubulin and collagen) have been proposed to have a role in mediating lung AMR. In one study, ECP was associated with a reduction in levels of circulating DSA, SAgs and proinflammatory cytokines (Baskaran, 2014). In 2012, the US Centers for Medicare & Medicaid Services determined that coverage for ECP in BOS post-lung transplant will be allowed only within the context of a study. One group showed no significant added benefit of ECP to standard AMR management (IA ± IVIG or ATG), with overall and graft survival still poor despite reduced mean fluorescence intensity of antibodies (Benazzo, 2020). For the treatment of pulmonary AMR, few studies have reported use of TPE (typically in combination with IVIG, and anti-B cell/plasma cell therapies) with variable results. One study used a protocol including TPE, IVIG, ±additional therapies (e.g., rituximab) and noted overall survival of approximately 60% at one year; 24% in the cohort had allograft failure or required re-transplant (Neuhaus, 2022). In regards to desensitization of patients who are highly alloimmunized and lung transplant waitlisted, several peri-operative multimodal approaches have been published. One group reported positive outcomes for DSA-positive patients who received TPE, plus IVIG and rituximab if allograft dysfunction occurred (Courtwright, 2019). Another published the long-term outcomes of sensitized lung transplant recipients ($N = 146$), showing similar rates of allograft and CLAD-free survival compared with unsensitized recipients ($N = 194$); sensitized recipients received a combination of pre- and post-operative TPE, IVIG, and ATG (Aversa, 2021).

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Technical notes

In a large CS of ECP in BOS a total of 12 cycles over 6 months were administered: weekly for 5 cycles, biweekly for 2 months (4 cycles), and then monthly for 3 months (3 cycles; Morrell, 2010).

Volume treated: ECP: varies;. TPE, 1 to 1.5 PV

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

Frequency: ECP: as above; TPE: daily to every other day

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. TPE to treat AMR typically consists of 3 to 6 exchanges. TPE timing and frequency for desensitization varies by protocol.

Keywords: lung rejection, photopheresis, bronchiolitis obliterans syndrome, pulmonary capillaritis, antibody mediated rejection, desensitization, lung transplantation, plasma exchange, plasmapheresis

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VACCINE-INDUCED IMMUNE THROMBOTIC THROMBOCYTOPENIA

Incidence: ChAdOx1 (1st dose) 1:26,500 to 127,300 doses; Ad26.COV.S 1:263,000 doses

Indication	Procedure		Category	Grade
Refractory*	TPE		III	2C
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	3 (26)	9 (11)

*Severe thrombocytopenia (<30 × 10^9/L) or cerebral venous sinus thrombosis, unresponsive to first-line management

Description

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a rare complication following adenoviral vector-based vaccinations. It was first described with the ChAdOx-1 (AstraZeneca) COVID-19 vaccine in February 2021, with a median time to presentation of 14 days post-vaccination (Pavord, 2021). Other terms used early after its recognition were thrombotic thrombocytopenic syndrome (TTS), vaccine-associated thrombosis and thrombocytopenia (VATT), and vaccine-induced prothrombotic immune thrombocytopenia (VIPIT). Patients presented with new thrombocytopenia and thrombotic complications. Incidence of VITT following the first dose of ChAdOx-1 ranged from 1 case per 26,500 vaccines (Norway) to 1 in 127,300 (Australia). Data from the United Kingdom suggests a lower risk after second dose (1 in 518,181). VITT was also identified in patients receiving the Ad26.COV2.S (Johnson & Johnson/Janssen) vaccine at an incidence of 1 case per 263,000. Two potential cases have been attributed to the mRNA-1273 (Moderna) vaccine (Su, 2021; Padmanabhan 2022); with the second found to have platelet-activating VITT antibodies with high optical density. Another case related to the BNT162b2 (Pfizer-BioNTech) vaccine has been reported (Bissola, 2022). Though some of these cases may be related to background rates of other thrombotic thrombocytopenic syndromes (See, 2022), VITT from non-adenoviral vaccines should be considered based on clinical presentation and confirmatory testing. Reports of *de novo* or recurrent vaccine-associated thrombotic thrombocytopenic purpura are not included (see Thrombotic microangiopathy, thrombotic thrombocytopenia purpura).

VITT pathophysiology is driven by formation of anti-platelet factor 4 (PF4) IgG antibodies (Scully, 2021). These platelet (and possibly pancellular) activating antibodies bind FcγIIa receptors and cause hemostatic derangement and thromboembolism. Animal studies also suggest a role of neutrophil extracellular traps formation (i.e., NETosis), with its inhibition associated with reduced thrombosis but not thrombocytopenia (Leung, 2022). Though its presentation is similar to heparin-induced thrombocytopenia (HIT), VITT antibodies and detection assays are heparin-independent. Thrombosis can occur at any site with VITT, with atypical and/or multi-site thrombosis common (e.g., cerebral, abdominopelvic, arterial). In a series of 220 confirmed or probable VITT cases, 50% had cerebral venous sinus thrombosis (CVST). The degree of thrombocytopenia varies widely, with median level of 47 × 10^9/L (Pavord, 2021). Diagnosis of suspected VITT is confirmed with a positive PF4/polyanion ELISA. Functional assays such as a PF4-supplemented serotonin release assay (SRA) are supportive but not required for diagnosis. Rapid HIT assays, in general, are not sensitive and should not be used (Nazy, 2021).

Current management/treatment

With presentation and pathophysiology similar to autoimmune HIT syndromes, first-line management of VITT consists of therapeutic anticoagulation and antibody inhibition. Most guidelines and experts recommend non-heparin anticoagulation (e.g., argatroban, bivalirudin, danaparoid, rivaroxaban, apixaban, fondaparinux); however, some reports noted no difference in adverse outcomes in those who received heparin (Pavord, 2021). Given its similarities to HIT, vitamin K antagonists (VKA, such as warfarin) are typically not used while the patient remains thrombocytopenic, though bridging to VKA could be done once thrombocytopenia resolves (Gabarin, 2022). Following platelet recovery, duration of anticoagulation depends on the thrombotic presentation and anticipated recurrence risk. As has been described in autoimmune HIT (Padmanabhan, 2017), upfront IVIG for antibody inhibition should be given acutely for presumed or confirmed VITT at a dose of 1 g/kg daily for two days. Additional doses may be effective and can directly inhibit antibodies using a modified SRA (Bourguignon, 2021).

In patients with a history of VITT, further vaccination, if desired, must be done cautiously, and only with an mRNA vaccine. Twenty-nine patients with a prior diagnosis of VITT (23 of whom were still taking anticoagulation) received an mRNA COVID-19 vaccine at a median of 16 weeks from diagnosis. None of these patients developed thrombotic complications and only a minority had transient reductions in platelet count (Schönborn, 2022).

Rationale for therapeutic apheresis

TPE has been used to directly remove the pathologic antibodies in VITT unresponsive to first-line management. The British Society of Haematology recommended TPE for severe thrombocytopenia (<30 × 10^9/L) or CVST, given the high risk of mortality in these patients. The overall survival of 17 such patients who received TPE was 90% compared to 50% for those not exchanged (Pavord, 2021). In one series, patients who received TPE had statistically significant reductions in their anti-PF4 ELISA optical densities with one polyspecific assay but not an IgG-specific platform. Those who received TPE also had slightly faster platelet recovery (Craven, 2022). One CS reported 3 such patients, managed with daily TPE until platelet recovery and no further thrombosis occurred. Two were exchanged with plasma alone, while one had half plasma and half albumin. One patient also received intermittent doses of IVIG, and one received rituximab after their last TPE. All 3 patients received argatroban and corticosteroids. One patient required left above-knee amputation for arterial thrombosis and ischemia; however, it was felt that TPE likely prevented more extensive limb involvement (Patriquin, 2021). Though CS and CRs suggest improvement in outcomes, the impact of apheresis on antibody reduction needs further study.

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Technical notes

Data regarding replacement fluid and frequency of TPE in VITT are limited; similar procedural considerations apply as with TPE for HIT, particularly the anticipated benefit of plasma over albumin as replacement (Jones, 2018). When possible, hemostatic monitoring during TPE should be considered to avoid subtherapeutic levels of anticoagulation, with monitoring based on the specific anticoagulant used.

Volume treated: 1 TPV **Frequency:** Daily until platelets normalize

Replacement fluid: Plasma ± albumin

Duration and discontinuation/number of procedures

In general, daily TPE should be continued until the platelet count normalizes ($\geq 150 \times 10^9$/L) and there is no further progression of thrombosis. Most CS and CRs reported 5 to 7 exchanges.

Keywords: vaccine-induced immune thrombotic thrombocytopenia (VITT), thrombotic thrombocytopenia syndrome (TTS), vaccine-induced prothrombotic immune thrombocytopenia (VIPIT), and/or vaccine associated thrombosis with thrombocytopenia (VATT), plasma exchange, plasmapheresis

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VASCULITIS, ANCA-ASSOCIATED

Incidence: 1 to 3/100,000/year (geographical, age, and ethnic differences)

Indication	Procedure		Category	Grade
Microscopic polyangiitis	TPE		III	1B
Granulomatosis with polyangiitis				
Eosinophilic granulomatosis with polyangiitis	TPE		III	2C
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	10 (1091)	5 (345)	NA	NA

Description

The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) comprise granulomatosis with polyangiitis (GPA; 25%-40%), microscopic polyangiitis (MPA; 48%-65%), and eosinophilic granulomatosis with polyangiitis (EGPA; 10%-20%). These diseases affect small- and medium-sized vessels and are characterized by multisystem organ involvement, commonly impacting the kidneys (70%; typically exhibiting rapidly progressive glomerulonephritis (RPGN) with high risk of end stage kidney disease (ESKD)), lungs (>50% at onset; can range from asymptomatic pulmonary lesions to life-threatening diffuse alveolar hemorrhage (DAH)), ear-nose-throat, joints, skin and nerves. Overlapping features between AAV subtypes occur. GPA is characterized by necrotizing granulomatous inflammation and is typically associated with cytoplasmic ANCA and antibodies to proteinase 3. GPA carries a higher risk for relapsing disease. MPA is characterized by vasculitis without granulomatous inflammation, and is most commonly associated with perinuclear ANCA and antibodies to myeloperoxidase. EGPA is rarely associated with RPGN or DAH. The presentation of the pulmonary-renal syndrome associated with ANCA can be clinically similar to anti-glomerular basement membrane (GBM) disease. When ANCA and anti-GBM are both present, the disease should be considered to represent anti-GBM disease (see *separate fact sheet*).

Current management/treatment

The treatment of all AAV subtypes is divided into two phases: induction of remission and, maintenance therapy given risk for relapse. Urgent treatment is required to prevent irreversible organ damage. The current standard of care for the induction phase is a combination of high-dose glucocorticoids with either cyclophosphamide or rituximab, which induces remission in up to 90% of patients. TPE has been included as an adjunctive therapy during induction in patients with significant kidney involvement and/or DAH, though the benefit has been challenged by the PEXIVAS study (Walsh, 2020). The mortality of AAV approaches 20% at 1 year, and is largely infection-related supporting a reduced steroid dose (50% of previous standard) based on RCT data from PEXIVAS demonstrating non-inferiority. There remains much practice variation and uncertainty for ideal steroid dosing in both induction and maintenance phases. Avacopan (a C5a receptor inhibitor) has been shown to be noninferior to oral prednisone for remission at 26 weeks, and superior to prednisone for sustained remission at week 52 in an RCT (Jayne, 2021). Maintenance treatment usually entails a gradual taper of steroids plus an additional immunomodulatory agent (azathioprine, mycophenolate mofetil, or rituximab) for 12 to 18 months.

Rationale for therapeutic apheresis

The cytotoxic role for ANCAs underlies the scientific rationale for therapeutic apheresis in the treatment of AAV. For decades, TPE has been considered an appropriate adjunctive therapy. Use of TPE for induction therapy in AAV with severe kidney involvement was first described as improving kidney function/dialysis independence in a RCT of 48 anti-GBM negative cases of RPGN with creatinine (Cr) >500 μmol/L (5.7 mg/dL; Pusey, 1991) then later confirmed by the MEPEX RCT (Jayne, 2007). Long-term follow-up from MEPEX (median 4 years) failed to show a net benefit of TPE on the composite outcome of death and ESKD (Walsh, 2013). Additionally, in other subsequent non-randomized CTs or CSs, the benefit of TPE was not always confirmed despite its acceptance into common practice. The addition of TPE in patients with severe kidney involvement remained a mainstay of induction therapy until the results of PEXIVAS, the largest RCT of TPE in AAV, failed to demonstrate a benefit of TPE on the composite primary outcome of ESKD and mortality at 12 months (Walsh, 2020).

PEXIVAS was an international RCT that enrolled 704 patients and assessed the effect of TPE as well as a reduced dose steroid regimen on the primary composite outcome of ESKD or death in patients with AAV with an eGFR<50 ml/min or with DAH. After induction with pulse steroids (IV) and cyclophosphamide (oral or IV) or rituximab, randomization to receive 60 mL/kg volume TPE or no TPEs and standard dose or reduced dose steroid regimen, with follow up for 2 to 7 years (median 2.9 years). Subgroup analysis of patients with Cr ≥5.7 mg/dL or DAH also failed to show a statistically significant benefit of TPE. However, review of supplemental data suggested outcomes may favor the TPE groups with DAH and when Cr ≥5.7 mg/dL; confidence intervals were large (i.e., PEXIVAS may be underpowered to detect differences in these subgroups). An accompanying editorial pointed out several issues regarding the generalizability of results (Derebail, 2020).

A subsequent systematic review and meta-analysis including 1060 participants with AAV found no impact of TPE on all-cause mortality, and data from seven trials with 999 total participants demonstrated a reduced risk of ESKD at 12 months (20% risk reduction); however, TPE was also associated with an increased risk for serious infections (Walsh, 2022). In a retrospective study of 427 cases of AAV with biopsy proven severe kidney involvement, a model predicting patients most likely to benefit from TPE was developed and favors those with increasingly elevated creatinine levels, high Brix score and crescentic Berden score on biopsy (Nezam, 2022). Further validation studies are needed to use this scoring system in clinic practice. The 2021 KDIGO guidelines continue to recommend consideration for TPE in select cases. The American College of Rheumatology (ACR) has recommended against the routine use of TPE in all patients with active glomerulonephritis, but notes that TPE can be considered for patients at higher risk for progression to ESKD who accept a potential increased risk for infection (Chung, 2021). The ACR guideline panel also recommended against the use of routine plasma exchange for DAH as TPE has not been able to demonstrate an improvement in mortality.

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Technical notes

Volume treated: 1 to 1.5 TPV

Frequency: Daily in DAH, typically every other day in absence of DAH

Replacement fluid: Albumin; plasma when DAH present

Duration and discontinuation/number of procedures

Median number of TPE is 7 over a median period of 14 days, up to 12 have been reported to result in further improvement in patients with severe kidney failure (Cr ≥5.7 mg/dL or on dialysis) or DAH (deLuna, 2015). Daily therapy should be considered in patients with severe DAH, tapered to every other day as clinical situation improves.

Keywords: ANCA, MPO-ANCA, PR3-ANCA, ANCA-associated vasculitis, granulomatosis with polyangiitis; Wegener's granulomatosis, diffuse alveolar hemorrhage, rapidly progressive glomerulonephritis, microscopic polyangiitis, pauci-immune glomerulonephritis, plasma exchange, plasmapheresis, immunoadsorption

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VASCULITIS, IgA

Incidence: 13 to 22/100,000/year with 1% developing rapidly progressive glomerulonephritis

Indication	Procedure		Category	Grade
Crescentic rapidly progressive glomerulonephritis Severe extra-renal manesfestations*	TPE		III	2C
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	9 (72)	24 (26)

*Cerebritis or severe gastrointestinal bleeding.

Description

Henoch-Schönlein purpura (HSP), now more commonly referred to as IgA vasculitis (IgAV) or IgA vasculitis with nephropathy (IgAVN) and in severe cases, crescent IgAVN (CreIgAVN), is the most common systemic vasculitis in childhood; 95% of IgAV cases occur in children. IgAV 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. IgAV is a systemic small vessel vasculitis characterized by deposition of IgA-containing immune complexes within tissues. In IgAVN it is thought that anti-IgA1 autoantibodies play a central role in the pathomechanism. Due to an inherited or acquired glycosylation defect in the mucosa of the GI, galactose deficient IgA1 (GdIgA1) is produced. These immune complexes are bound to the transferrin receptors of the mesangium causing mesangial cell proliferation and activation of neutrophils. IgA from serum of patients with IgAV has been found to bind to human endothelial cells in vitro, supporting the presence of IgA anti-endothelial cell antibodies (AECA). It has been hypothesized that microorganisms have similar antigenic structures as human vessel walls. Infection with these microorganisms could lead to the production of cross-reactive AECA, although no specific microorganism has been identified in IgAV yet (Heineke, 2017).

All patients develop palpable purpura. In the skin, immune complex deposits lead to subepidermal hemorrhages and small vessel necrotizing vasculitis producing the purpura. One-quarter to one-half of cases involve the kidney. 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 CS. 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 end stage kidney disease (ESKD) range from 15% to 30% over 15 years of age 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 gastrointestinal bleeding.

Current management/treatment

Treatment is supportive care including hydration, rest, and pain control. In patients with severe kidney involvement (CresIgAVN) or severe symptoms of vasculitis, treatment can also include corticosteroids with or without immunosuppressants such as cyclophosphamide, azathioprine, or cyclosporine and IVIG. If ESKD develops, kidney transplantation may be necessary.

Rationale for therapeutic apheresis

The rationale for TPE is the removal of IgA1-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 IgAV 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 IgAV. Numerous CRs have demonstrated some success in severely ill patients with IgAV or IgAVN and severe bleedings of the lung, GI tract and in cerebritis.

Limited but encouraging data suggest TPE may benefit patients with severe disease. Seven CRs and 8 CS totaling 67 patients have examined the use of TPE in treating CreIgAVN. In 27 of these patients, concurrent immunosuppressive therapy was not given. In these patients treated with only TPE, 21 had complete resolution of their kidney disease, 2 had persistent hematuria, 1 had persistent proteinuria, and 2 progressed to ESKD. The remaining patient was an adult who had resolution of kidney disease with TPE but recurrence following discontinuation of TPE. The patient subsequently had complete resolution of kidney 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 kidney disease.

Technical notes

Replacement fluid has varied depending upon the clinical situation with the final portion consisting of plasma in the presence of severe bleeding.

Volume treated: 1 to 1.5 TPV

Frequency: 4 to 11 over 21 days

Replacement fluid: Albumin or plasma

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Duration and discontinuation/number of procedures

In severe manifestations, the course of therapy has ranged from 1 to 11 TPE daily with discontinuation of TPE upon resolution of symptoms. In CreIgAVN, longer courses of therapy have occurred with therapy discontinued with improvement in kidney function as determined by creatinine measurement.

Keywords: plasma exchange, IgA vasculitis, Henoch-Schönlein purpura, rapid progressive glomerulonephritis

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VASCULITIS, OTHER

Incidence: PAN: 5 to 77/1,000,000; Kawasaki disease: 18 (United States) -359 (Japan)/100,000; MIS-C: 2 to 10/100,000				
Indication	**Procedure**		**Category**	**Grade**
Hepatitis B polyarteritis nodosa	TPE		II	2C
Kawasaki disease multisystem inflammatory syndrome in children	TPE		III	2C
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Hepatitis B polyarteritis nodosa	0	0	1 (115)	NA
Kawasaki disease	0	1 (105)	16 (239)	8 (9)
Multisystem inflammatory syndrome in children	0	0	7 (54)	7 (7)

PAN = polyarteritis nodosa; MIS-C = multisystem inflammatory syndrome in children.

Description

Vasculitis involves inflammation in blood vessels including arteries, veins, and capillaries. There are other types of vasculitis addressed in this issue (see *separate fact sheets*). Behçet's disease is a rare immune-mediated systemic vasculitis that can involve blood vessels of all sizes and can affect both the arterial and venous vessels. Use of TPE and granulocyte and monocyte adsorption apheresis have been reported in small CS and CRs but there has been no new research on apheresis in this area since 2015. Refer to the 2019 JCA special issue for more information about this indication.

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis predominantly of adults that affects medium-sized arteries, sharing many characteristics of microscopic polyangiitis, however, it is not associated with ANCA antibodies and it spares the pulmonary and glomerular vessels. It can be idiopathic, or occur in the setting of a rare autosomal recessive mutation of adenosine deaminase 2 (ADA2), familial Mediterranean fever, or hepatitis B virus (HBV-PAN). In HBV-PAN, the endothelial vascular inflammatory lesions result from immune complex deposition, resultant complement activation, and increase in inflammatory cytokines. With increasing HBV vaccination rates, new cases of HBV-PAN are now rare. Idiopathic PAN is a category IV indication described in the JCA 2019 Special Edition.

Kawasaki disease (KD) is an acute febrile illness of childhood associated with systemic vasculitis mainly of medium-sized arteries with a predilection for coronary arteries. The pathogenesis of KD has not been fully elucidated but it is thought to be an exaggerated immune response in genetically predisposed children in whom environmental factors, such as infections, could be a potential trigger. Activation of innate and adaptive immune systems is thought to be a central feature, and elevated levels of IL-1β, IFN-γ, IL-6, IL-8, and TNF-α have been shown to activate endothelial cells damaging the intima leading to coronary artery lesions.

Multisystem inflammatory syndrome in children (MIS-C) is a rare but severe hyperinflammatory disease that can lead to cardiovascular collapse and multiorgan failure, occurring 2 to 6 weeks following COVID-19 infection. MIS-C shares many clinical features of KD or toxic shock syndrome, but also includes severe abdominal pain, shock, cardiac dysfunction, neurologic and respiratory findings, lymphopenia, and evidence of recent COVID-19 infection. Mechanisms of myocardial damage in MIS-C have not been well characterized, though systemic inflammation, acute viral myocarditis, hypoxia, stress cardiomyopathy, and ischemia have been postulated. MIS-C more commonly develops in older children (>8 years) while KD is more common in those <3 years.

Current management/treatment

Untreated PAN can be rapidly progressive and fatal, with a 20% mortality rate in idiopathic cases. The Five-Factor Score (FFS) has been used for PAN for evaluating disease severity and prognosis. Patients with renal symptoms, gastrointestinal tract involvement, cardiomyopathy, central nervous system involvement, loss of >10% of body weight, and age >50 years may have poor prognosis and require maintenance treatment. For HBV-PAN, treatment includes anti-viral medications, an initial short course of glucocorticoids, and TPE.

In KD the goal of therapy is to suppress the vasculitis before the development of coronary artery lesions (CALs), which can be detected as early as days 7 to 10. First line therapy includes the administration of a single high dose IVIG (2 gm/kg), which has been shown to reduce the risk of CALs. Aspirin is included in first line therapy, reducing mortality from 2% to 0.2%; however, monotherapy with aspirin is not sufficient to prevent CALs. Up to 20% will be refractory to a single dose of IVIG, and even after subsequent doses of IVIG, 5% to 10% of children remain IVIG resistant and are at higher risk for developing CALs. Refractory KD is typically defined as persistence of fever and the inflammatory response. For patients who are IVIG-resistant, intravenous methylprednisolone, infliximab, cyclosporine, ulinastatin, and TPE have been used as alternate therapies.

There are no randomized trials evaluating therapies for MIS-C, however, the mainstay of therapy includes immunomodulation (IVIG and/or corticosteroids), anticoagulation, and management of shock. Approximately 30 to 80% of patients do not respond to IVIG alone and may require adjunctive immunomodulatory therapy to control inflammation. High dose anakinra (recombinant IL-1 receptor antagonist) is recommended in those resistant to IVIG and steroids. Tocilizumab and TPE have also been used in resistant cases with severe features.

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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 agents has been shown to be effective in several CS for HBV-PAN (Guillevin, 2005).

TPE has been used in Japan for over 20 years in cases of KD refractory to IVIG, and has been approved as alternative therapy since 2012. The first large case series demonstrating benefit of TPE for IVIG resistant KD evaluated 105 patients, 46 of which were treated with TPE (Mori, 2004). In those whose coronary artery dilatation started before TPE was initiated, the residual sequelae rate was 30% (Hokosaki, 2012). Infliximab in combination with TPE may further suppress CAL formation in KD refractory to IVIG (Sonoda, 2014). A small study of 16 patients found that patients who received infliximab prior to TPE required fewer procedures and had a greater drop in CRP levels, though there were no differences in CALs between the two groups (Shimada, 2020).

TPE for MIS-C is thought to reduce cytokines and other inflammatory mediators, and replenish missing plasma factors in cases where plasma is used for replacement. A retrospective analysis of 18 cases of severe MIS-C demonstrated improved 28 day mortality, shortened length of hospital stay and less ionotropic and ventilatory support when TPE was applied early in course (within 5 days of admission, $n = 13$), compared to later (Katlan, 2022).

Technical notes

Volume treated: 1 to 1.5x TPV **Frequency:** Varies

Replacement fluid: Albumin, plasma

Duration and discontinuation/number of procedures

For HBV-PAN, 9 to 12 TPEs (2-3 per week) have been used, typically with albumin replacement. For KD refractory to IVIG, TPE is generally performed daily for 3 days or until fever and inflammatory response subsides, with a maximum of 5 days, using albumin as the typical replacement solution. In severe MIS-C, 1 to 11 TPEs have been reported, typically on consecutive days until fever and inflammatory response subsides, with some reports using plasma for replacement.

Keywords: vasculitis, Kawasaki disease, MIS-C, polyarteritis nodosa, plasma exchange

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VOLTAGE-GATED POTASSIUM CHANNEL ANTIBODY RELATED DISEASES

Incidence: rare				
Procedure	**Category**		**Grade**	
TPE/IA	II		1B	
# reported patients: 100 to 300	**RCT**	**CT**	**CS**	**CR**
	0	1 (21)	11 (96)	NA

Description

Voltage-gated potassium channels (VGKCs) are membrane proteins expressed by a wide range of cells and are important in the control of membrane excitability in the peripheral and central nervous system. Integral parts of the VGKC-complex are the target antigens for VGKC antibodies, including especially leucine-rich, glioma inactivated 1 (LGI1), and contactin-associated protein-2 (CASPR2). Recent research has confirmed that most VGKC antibodies that are not directed at CASPR2 or LGI1 (so-called double-negative VGKC antibodies) lack pathogenic potential, as they often target intracellular epitopes. Double-negative VGKC antibodies are encountered in approximately 5% of healthy controls. This should prompt clinicians to use LGI1 and CASPR2 antibodies as first-line testing. LGI1 and CASPR2 antibodies mostly belong to the IgG4 subclass, which does not activate complement and cannot bind to inhibitory Fcγ receptor to activate cellular and complement-mediated immune responses, the key functions inhibited by IVIg. VGKC complex antibodies were initially described in adults with limbic encephalitis, which clinically represents a prototype of antibody mediated autoimmune encephalitis (AME) if associated with N-methyl-D-aspartate receptor (NMDAR)-antibodies (Dalmau, 2018; see *separate fact sheet*). LGI1-AME is the second most common AME. Patients who test positive for VGKC autoantibodies are frequently positive for both LGI1 and CASPR2 antibodies. Antibodies also appear in cerebrospinal fluid in the majority of patients.

VGKC-complex antibodies are implicated in the pathogenesis of LGI1/CASPR2-AME, acquired peripheral nerve hyperexcitability syndromes with considerable clinical overlap, that is, acquired neuromyotonia (NMT), cramp-fasciculation syndrome, Isaac's syndrome (characterized by peripheral nerve hyperexcitability with muscle twitching, myokymia, muscle hypertrophy, dysautonomia, and sometimes neuropathic pain and paresthesia) and Morvan's syndrome (MVS). In particular, Isaac's syndrome and MVS may exhibit paraneoplastic appearance (e.g., thymomas) with low response to immunotherapies and clinical symptoms preceding occurrence of a malignancy. Therefore, oncological screening is generally recommended every 6 months for 4 years following diagnosis. AME-syndromes to a certain extent differ between anti-LGI1 and anti-CASPR2. Typical for anti-LGI1 are facio-brachial dystonic seizures, cognitive impairment, amnesia, psychosis, and hyponatremia (65%-75%); typically for anti-CASPR2 are cerebellar ataxia, neuromyotonia, neuropathic pain, and autonomic dysfunction, but not hyponatremia. Peripheral nerve hyperexcitability without exertional weakness, and muscle stiffness are chief manifestations of NMT. MVS typically presents with NMT, neuropsychiatric features, autonomic dysfunction, and neuropathic pain, thus overlapping with AME or NMT. Overall, the long-term prognosis is highly variable ranging from spontaneous remission to chronic, or even fatal courses.

Current management/treatment

The wide spectrum of clinical presentations makes differential diagnosis complex and many patients suffer from the delayed recognition of these conditions. Since the discovery of VGKC antibodies, some conditions, in particular encephalitis, previously considered only for symptomatic treatment, have received better explanation of pathogenesis due to disruption of protein–protein interactions affecting VGKC related signal transduction pathways in the central and peripheral nervous system. Thus, different immunotherapies have been used in VGKC-complex antibody associated diseases, including the entire multimodal therapeutic armamentarium against autoantibody-associated diseases (e.g., steroids, IVIG, therapeutic apheresis (TPE, or IA), immunosuppressive drugs and B cell depleting drugs), in addition to symptomatic treatment (e.g., anti-seizure medication). Due to the overall low incidence of VGKC-complex antibody associated diseases the evidence for all options is limited. Application of steroids is regarded fundamental in any combination therapy. For AME in general, thus including VGKC-AME, TPE, or if available IA, is increasingly used as first-line treatment in combination with steroids, and symptomatic drug treatment. Acute therapy for the other anti-LGI1/CASPR2-associated syndromes usually consists of steroids and/or IVIG. TPE or IA is considered as a second-line option. Of note, most recent CS reported that early diagnosis and initiation of immunomodulation therapy led to better control of symptoms such as seizures, which are often resistant to conventional anti-seizure medications. In general, non-paraneoplastic syndromes show a better response to immunomodulating therapies. Due to the high variability of symptoms, response to treatment, and outcome, treatment needs to be individualized.

Rationale for therapeutic apheresis

There is a clear rationale for the use of TPE or IA as part of the multimodal immunomodulating therapeutic approach. The rapid decrease of LGI1/CASPR2 antibodies with TPE or IA is associated with clinical improvement. An open label prospective study used an immunotherapy protocol consisting of IV methylprednisolone (1 g/day for 3 days), TPE of 5 treatments over 7 to 10 days typically after completion of IV methylprednisolone, followed by IVIG (2 g/kg over 5 days) and maintenance therapy with oral prednisolone (1 mg/kg). Using this regimen on 9 patients (first 3 patients also received mycophenolate mofetil (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 magnetic resonance imaging, and significantly decreased VGKC antibody levels (Wong, 2010). In a two-center retrospective analysis of 10 patients with VGKC-AME, TPE was administered in 7 patients in conjunction with steroids and IVIG. Four of 7 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 (Vincent, 2004). In a CS of 5 retrospectively identified patients with neurological symptoms and VGKC antibodies treated with TPE, there was a durable clinical response in 3 of these patients

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(Jaben, 2012). Moreover, in some of the reports, TPE was used as a maintenance therapy to control symptoms and prevent relapsing acute attacks. 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. Successful use of IA was reported for VGKC-AME cases including a case control study comparing TPE and tryptophan-IA (Heine, 2016), thus avoiding replacement of human plasma products including their potential side effects and cost.

Technical notes

Volume treated: 1 to 1.5 TPV with TPE; 2 to 2.5 liters for tryptophan-IA (manufacturer's recommendation); up to 2.5 TPV with regenerative immunoadsorption columns

Frequency: 5 to 10 treatments with TPE or IA over 7 to 14 days adjusted to the individual course

Replacement fluid: TPE: albumin; IA: NA

Duration and discontinuation/number of procedures

Anti-LGI1/CASPR2 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. However, response of clinical symptoms has been used to determine treatment course.

Keywords: voltage-gated potassium channel antibodies, LGI1, CASPR2, Morvan's syndrome, Isaac's syndrome, neuromyotonia, limbic encephalitis, autoimmune encephalitis, plasma exchange, immunoadsorption

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WILSON DISEASE, FULMINANT

Incidence: 1/30,000 to 40,000; ~1% of the population are carriers

Procedure	Category		Grade	
TPE	I		1C	
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	1 (37)	6 (31)	29 (30)

Description

Wilson disease is an autosomal recessive genetic disorder resulting from a mutation in the *ATP7B* gene, which encodes a copper transporting ATPase protein, leading to impaired biliary copper excretion, resulting in copper accumulation in the liver, brain, cornea, and kidney. The incorporation of copper into ceruloplasmin is also impaired. The disease usually presents between ages 5 to 35 years. Children present with asymptomatic 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. Heart involvement includes cardiomyopathy, left ventricular diastolic dysfunction, elevated troponin, rhythm or conduction abnormalities, and dysautonomia; MRI occasionally shows heart abnormalities consistent with global and regional myocardial fibrosis. The appearance of Kayser-Fleischer rings (copper deposits in the outer rim of the cornea) and direct antiglobulin test (DAT) negative hemolytic anemia are relatively common. The hemolysis appears to be primarily due to copper-induced oxidant stress to RBC enzyme pathways and membrane damage. ALF is typically accompanied by hemolytic crisis and multi-organ 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-hour urinary copper excretion, and elevated serum copper. The gold standard for diagnosis is a liver biopsy showing elevated copper content. Genetic testing for *ATP7B* gene mutations 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 metallothionein, which reduces dietary and enterohepatic absorption of copper. It is the therapy of choice for patients who are asymptomatic, pediatric, pregnant, or with hepatitis or cirrhosis, but without evidence of hepatic decompensation or neurologic/psychiatric symptoms. Chelation therapy (penicillamine, trientine) increases urinary copper excretion. Trientine has replaced penicillamine as the primary chelator due to less toxicity. Penicillamine should always be accompanied by pyridoxine. Chelation can be used as a temporizing agent to treat the enormous release of copper into the blood stream in ALF with kidney failure; however, substantial removal is not achieved for at least 1 to 3 months. Copper reduction therapy must be life-long, and there are new strategies aimed at improving adherence and outcomes, including once daily chelation dosing. Other methods have been used to reduce copper load to stabilize patients including hemofiltration, albumin dialysis, and the Molecular Adsorbents Recirculating System (MARS). LT is potentially curative, reversing most of the clinical and biochemical pathological manifestations of the disease within months, and is the mainstay of therapy for patients with ALF. Disease severity is estimated using one of various existing prognostic scores, which are based on a combination of laboratory values, most commonly LFTs and coagulation status (international normalized ratio [INR]/prothrombin time [PT]), New Wilson's index, Child-Pugh score, and model for end-stage liver disease (MELD) score. The AARC-ACLF (APASL ACLF Research Consortium-Acute on Chronic Liver Failure) score and the CLIF-SOFA (Chronic Liver Failure-Sequential Organ Failure Assessment) score have each been shown to be excellent predictors of outcome in decompensated Wilson disease (Alam, 2019).

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 to rapidly remove significant amounts of copper from the circulation, an average of 20 mg per TPE treatment. Decreased serum copper may decrease hemolysis, prevent progression of kidney 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 has been utilized as a bridge to LT. Reports have shown TPE combined with chelating agents improves ALF and may eliminate the need for LT (Camarata, 2020; Fang, 2021). A CT of high volume TPE (HV-TPE: defined as >1.5 plasma volumes) treatment of Wilson disease in 37 pediatric patients with ALF showed transplant-free survival at 90 days was 47% (9 of 19 patients) in the HV-TPE group versus 17% (3 of 18 patients) in the standard medical treatment group ($P = .049$; Pawaria, 2021).

Technical notes

Plasma replacement rapidly corrects coagulopathy. Plasma/albumin combination is also possible. Use of albumin alone will worsen coagulopathy.

Volume treated: 1 to 1.5 TPV

Frequency: Daily or every other day

Replacement fluid: Plasma, albumin

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Duration and discontinuation/number of procedures

Serum copper reduction in most CRs was achieved rapidly and maintained after the first two treatments. However, the total number of TPE performed was variable (1-11), depending on LT availability or recovery. The majority of protocols involved daily TPE X 3 to 5 treatments followed by every other day TPE (depending on clinical and laboratory presentation and response to treatment). Specific laboratory tests for the disease (e.g., serum copper, 24-hour urinary copper excretion) are not helpful to guide efficacy and frequency of treatment; judgment is based on clinical parameters and routine testing (i.e., improved encephalopathy, LFTs, and controlled hemolysis).

Keywords: Wilson disease, liver transplantation, copper, plasma exchange

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