

Overview of the ASFA Guidelines on the Use of Therapeutic Apheresis in Clinical Practice

Focus on Atypical Hemolytic Uremic Syndrome (Atypical-HUS)

In 2019, the American Society for Apheresis (ASFA) released the eighth edition of its special issue on therapeutic apheresis in clinical practice. These updated guidelines help practitioners choose when to initiate therapy and, equally important, when to reduce or stop apheresis practices where there is questionable benefit with no established evidence, or even harm. The updated guidelines aim to provide the most current and best available evidence concerning apheresis practices and are based on case reports, case series, cohort studies, and randomized, controlled trials focused on many of the indications for which apheresis is used.

This information is expected to appeal to practitioners who may need to utilize apheresis occasionally for treating their patients for associated diseases.

KEY TAKEAWAYS

- Patients with atypical-HUS should receive therapeutic plasma exchange (TPE) only when appropriate.
- Apheresis guidelines encourage the appropriate use of apheresis based on the available evidence and direct practitioners in their decision-making. Differential diagnosis of TMA is critical because TPE is the best course of treatment for thrombotic thrombocytopenic purpura (TTP), but its efficacy in most cases of atypical-HUS is limited.
- When practitioners suspect atypical-HUS, they need to consider the complement mutations and that TPE isn't the recommended treatment for the majority of cases based on the categorization and grading of atypical-HUS as seen in the provided tables from the ASFA 2019 Special Issue Guidelines.

This document uses the term *atypical-HUS* while the ASFA 2019 Special Issue uses the term *complement-mediated thrombotic microangiopathy*. Complement may play a role in many thrombotic microangiopathies (TMAs), including atypical-HUS.¹



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| Timing of Discontinuation of TPE

When considering the guidelines, there is a role for TPE when the initial diagnosis is unknown or if atypical-HUS is not suspected in a patient with newly diagnosed TMA. Once atypical-HUS (complement-mediated thrombotic microangiopathy) is suspected, it is assumed that the patient may have an underlying genetic abnormality and appropriate management is recommended.¹

| The Evolution of Classification

Historically, if TMA was suspected and a diagnosis of TTP or Shiga toxin-producing *E coli* hemolytic uremic syndrome (STEC-HUS) was excluded, the TMA-associated disorder was commonly labeled as atypical-HUS. Over the last two decades, the pathophysiology of many individual diseases presenting with TMA have been identified.²

Atypical-HUS has been categorized in the ASFA Guidelines as complement-mediated thrombotic microangiopathy. Similarly, as a result of increasing insights into the pathogenesis of complement-mediated TMA as well as clinical trial data, TPE is not recognized as a first- or second-line therapy for atypical-HUS in the majority of cases. It is now classified as a category III indication, meaning the optimum role of TPE is not established in most cases, except in patients with Factor H autoantibody when it is category I.¹

TPE is not recognized as the first- or second-line therapy for atypical-HUS in the majority of cases.

The majority of TMA disorders have been named alphabetically (see Table 3), following the prefix

“thrombotic microangiopathy” (eg, thrombotic microangiopathy, complement-mediated) so that the indication would be easier for apheresis practitioners to locate in the ASFA Guidelines. Now that all the TMA-associated conditions are listed together, practitioners can easily consider alternate etiologies, especially in circumstances where there may be overlap in a single patient.¹

Atypical-HUS has been categorized as Category III by the ASFA Guidelines, meaning that the optimum role of TPE is not established for most patients and decision-making should be individualized.

| The Removal of Isolated *MCP* (CD46) Complement Mutation Guidance

The updated 2019 ASFA Guidelines removed guidance for membrane cofactor protein (*MCP*) mutations due to the lack of effect of TPE on outcomes and knowledge that *MCP* (CD46) does not circulate in the peripheral blood. The updated ASFA Guidelines also renamed TTP as thrombotic microangiopathy, thrombotic thrombocytopenic purpura; it is now listed with the other TMA indications.¹

| The Crucial Role of ADAMTS13 in Differential Diagnosis of TMAs

If the ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13) test results are >5% to 10%, the STEC test is negative, TMA is persistent, and there is multi-organ involvement, the diagnosis is more likely to be atypical-HUS (complement-mediated TMA) and the practitioner should consider discontinuing TPE, especially if there is no improvement in certain clinical parameters.¹⁻³ ADAMTS13 activity and antibody testing should

be a standing lab order prior to the initiation of TPE because analysis of ADAMTS13 activity may be inaccurate once plasma has been provided.¹⁻⁴

If you are doing daily TPE for more than 3 to 5 days and you do not see improvement (ie, normalized platelet count and lactate dehydrogenase (LDH) level and reduced serum creatinine level by 25%) and your ADAMTS13 activity is more than 5% to 10%, TPE should be discontinued and other management options considered.⁵ (Many centers attempt to ascertain a PLASMIC Score to differentiate between TTP and alternate pathologies.)¹

While waiting for ADAMTS13 results, a platelet count of $>30,000/\text{mm}^3$ and/or serum creatinine >1.7 to 2.3 mg/dL mostly excludes a diagnosis of TTP.^{4,6}

You do not need to wait to verify genetic mutations in order to make a diagnosis of atypical-HUS.^{1,3,4} Genetic testing is a prognostic tool to help guide long-term patient management, particularly since genetic mutations in atypical-HUS have not been identified in 30% to 50% of patients.^{7,8} Testing for anti-complement factor H (CFH) autoantibodies is also recommended.

ADAMTS13 activity and antibody testing should be a standing lab order prior to the initiation of TPE.¹

—ASFA Guidelines

| Understanding Atypical-HUS

Approximately 60% of atypical-HUS cases involve complement genetic defects, including CFH, MCP, and factor I (CFI). CFH mutations occur in 20% to 30% of patients, and acquired

complement dysregulation has been reported in 6% to 10% of cases due to anti-CFH autoantibodies.¹

With the current understanding of the pathological mechanism in atypical-HUS, use of TPE becomes somewhat limited.¹

—ASFA Guidelines

Genetic penetrance is approximately 50%. In 69% of patients with atypical-HUS, the disease can be unmasked by various triggers, such as diarrhea/gastroenteritis, upper respiratory tract infections, malignant hypertension, pregnancy-associated and/or transplant-associated glomerulopathy, systemic disease (eg, systemic lupus erythematosus), and malignancy.⁹

Atypical-HUS is a disease with a diagnosis of exclusion: negative for STEC-HUS (thrombotic microangiopathy, infection associated) and no criteria for TTP (per ADAMTS13 activity $>5\%$ - 10%). Historically, 65% of all patients with atypical-HUS die, require dialysis, or have end-stage renal disease during the first year.^{1,3}

Empiric TPE in many forms of severe undiagnosed TMA is still recommended while awaiting the ADAMTS13 result. When TPE is started prior to a confirmed diagnosis, follow-up on laboratory findings is recommended so the appropriate treatment pathway can be applied. The rationale for TPE use is that it can effectively remove the autoantibody or mutated circulating complement regulators, while replacing absent or defective complement regulators. The guidelines state, “With the current understanding of the pathological mechanism in atypical-HUS, use of TPE becomes somewhat limited.”¹

| Dr Connelly-Smith is a member of ASFA and a coauthor of the apheresis guidelines



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Learn more about atypical-HUS at:
aHUSSource.com/physician



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TABLES

The following information is extracted from the 2019 ASFA Guidelines.

The chart of **Thrombotic Microangiopathy, Complement Mediated** covers its incidence, condition, procedure, recommendation, and category.

Table 1 summarizes all ASFA categories and grades of recommendation.

Table 2 lists category descriptions.

Table 3 covers grading recommendation based on the Grades of Recommendation Assessment, Development and Evaluation system, which takes methodological quality of supporting evidence into account.

THROMBOTIC MICROANGIOPATHY, COMPLEMENT MEDIATED

Incidence: <7/1,000,000	Indication Factor H autoantibody Complement factor gene mutations	Procedure TPE TPE	Recommendation Grade 2C Grade 2C	Category I III
# reported patients: >300	RCT	CT	CS	CR
Factor H autoantibody	0	0	5(126)	NA
Complement factor gene mutations*	0	1(31)	22(361)	NA

*These studies include some patients who were not tested or were tested and found negative for complement factor gene mutations.

TABLE 1 | Category Definitions for Therapeutic Apheresis

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
III	Optimum role of apheresis therapy is not established. Decision-making should be individualized.
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.

IRB=Institutional Review Board.

TABLE 2 | 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 recommendation; other alternatives may be equally reasonable

RCT=randomized controlled trial. Adapted from Guyatt, 2006;2008.

TABLE 3 | Category and Grade Recommendations for Therapeutic Apheresis

Disease	TA modality	Indication	Category	Grade	Page
Acute disseminated encephalomyelitis (ADEM)	TPE	Steroid refractory	II	2C	187
Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome)	TPE	Primary treatment	I	1A	189
	IA	Primary treatment	I	1B	
Acute liver failure	TPE-HV		I	1A	191
	TPE		III	2B	
Age-related macular degeneration, dry	Rheopheresis	High-risk	II	2B	193
Amyloidosis, systemic	β2-microglobulin column	Dialysis-related amyloidosis	II	2B	195
	TPE	Other causes	IV	2C	
Anti-glomerular basement membrane disease (Goodpasture syndrome)	TPE	Diffuse alveolar hemorrhage (DAH)	I	1C	197
	TPE	Dialysis-independence	I	1B	
	TPE	Dialysis-dependence, no DAH	III	2B	
Atopic (neuro)dermatitis (atopic eczema), recalcitrant	ECP		III	2A	199
	IA		III	2C	
	TPE/DFPP		III	2C	
Autoimmune hemolytic anemia, severe	TPE	Severe cold agglutinin disease	II	2C	201
	TPE	Severe warm autoimmune	III	2C	
Babesiosis	RBC exchange	Severe	II	2C	203
Burn shock resuscitation	TPE		III	2B	205
Cardiac neonatal lupus	TPE		III	2C	207
Catastrophic antiphospholipid syndrome (CAPS)	TPE		I	2C	209
Chronic focal encephalitis (Rasmussen encephalitis)	TPE		III	2C	211
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	TPE/IA		I	1B	213
Coagulation factor inhibitors	TPE		III	2C	215
	IA		III	2B	
Complex regional pain syndrome	TPE	Chronic	III	2C	217

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Disease	TA modality	Indication	Category	Grade	Page
Cryoglobulinemia	TPE	Severe/symptomatic	II	2A	219
	IA	Severe/symptomatic	II	2B	
Cutaneous T-cell lymphoma (CTCL); Mycosis fungoides; Sézary syndrome	ECP	Erythrodermic	I	1B	221
	ECP	Non-erythrodermic	III	2C	
Dilated cardiomyopathy, idiopathic	IA	NYHA II-IV	II	1B	223
	TPE	NYHA II-IV	III	2C	
Erythropoietic protoporphyria, liver disease	TPE		III	2C	225
	RBC exchange		III	2C	
Familial hypercholesterolemia	LA	Homozygotes	I	1A	227
	LA	Homozygotes	II	1A	
	TPE	Homozygotes/ Heterozygotes	II	1B	
Focal segmental glomerulosclerosis (FSGS)	TPE/IA	Recurrent in kidney transplant	I	1B	229
	LA	Recurrent in kidney transplant/Steroid resistant in native kidney	II	2C	
	TPE	Steroid resistant in native kidney	III	2C	
Graft versus host disease (GVHD)	ECP	Acute	II	1C	231
	ECP	Chronic	II	1B	
Hemolysis, elevated liver enzymes, and low platelets syndrome (HELLP syndrome)	TPE	Postpartum	III	2C	233
	TPE	Antepartum	IV	2C	
Hemophagocytic lymphohistiocytosis (HLH); Hemophagocytic syndrome; Macrophage activating syndrome	TPE		III	2C	235
Heparin-induced thrombocytopenia and thrombosis (HIT/HITT)	TPE	Pre-cardiopulmonary bypass	III	2C	237
	TPE	Thrombosis	III	2C	
Hereditary hemochromatosis	Erythrocytapheresis		I	1B	239
Hyperleukocytosis	Leukocytapheresis	Symptomatic	II	2B	241
	Leukocytapheresis	Prophylactic or secondary	III	2C	
Hypertriglyceridemic pancreatitis	TPE/LA	Severe	III	1C	243
	TPE/LA	Prevention of relapse	III	2C	
Hyperviscosity in hypergammaglobulinemia	TPE	Symptomatic	I	1B	245
	TPE	Prophylaxis for rituximab	I	1C	

Disease	TA modality	Indication	Category	Grade	Page
IgA nephropathy (Berger's disease)	TPE	Crescentic	III	2B	247
	TPE	Chronic progressive	III	2C	
Immune thrombocytopenia (ITP)	TPE/IA	Refractory	III	2C	249
Inflammatory bowel disease	Adsorptive cytapheeresis	Ulcerative colitis/Crohn's disease	III	1B	251
	ECP	Crohn's disease	III	2C	
Lambert-Eaton myasthenic syndrome	TPE		II	2C	253
Lipoprotein(a) hyperlipoproteinemia	LA	Progressive atherosclerotic cardiovascular disease	II	1B	255
Malaria	RBC exchange	Severe	III	2B	257
Multiple sclerosis	TPE	Acute attack/relapse	II	1A	259
	IA	Acute attack/relapse	II	1B	
	TPE	Chronic	III	2B	
	IA	Chronic	III	2B	
Myasthenia gravis	TPE/IA	Acute, short-term treatment	I	1B	261
	TPE/IA	Long-term treatment	II	2B	
Myeloma cast nephropathy	TPE		II	2B	263
Nephrogenic systemic fibrosis	ECP/TPE		III	2C	265
Neuromyelitis optica spectrum disorders (NMOSD)	TPE	Acute attack/relapse	II	1B	267
	IA	Acute attack/relapse	II	1C	
	TPE	Maintenance	III	2C	
N-methyl-D-aspartate receptor antibody encephalitis	TPE/IA		I	1C	269
Overdose, envenomation, and poisoning	TPE	Mushroom poisoning	II	2C	271
	TPE	Envenomation	III	2C	
	TPE	Drug overdose/poisoning	III	2C	
Paraneoplastic neurological syndromes	TPE/IA		III	2C	273
Paraproteinemic demyelinating neuropathies; Chronic acquired demyelinating polyneuropathies	TPE	IgG/IgA/IgM	II	1B	275
	TPE	Anti-MAG neuropathy	III	1C	
	TPE	Multiple myeloma	III	2C	
	TPE	Multifocal motor neuropathy	IV	1C	
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS); Sydenham's chorea	TPE	PANDAS, exacerbation	II	1B	277
	TPE	Sydenham's chorea, severe	III	2B	

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Disease	TA modality	Indication	Category	Grade	Page
Pemphigus vulgaris	TPE	Severe	III	2B	279
	ECP/IA	Severe	III	2C	
Peripheral vascular diseases	LA		II	1B	281
Phytanic acid storage disease (Refsum's disease)	TPE/LA		II	2C	283
Polycythemia vera; Erythrocytosis	Erythrocytapheresis	Polycythemia vera	I	1B	285
	Erythrocytapheresis	Secondary erythrocytosis	III	1C	
Post-transfusion purpura (PTP)	TPE		III	2C	287
Progressive multifocal leukoencephalopathy (PML) associated with natalizumab	TPE		III	1C	289
Pruritus due to hepatobiliary diseases	TPE	Treatment resistant	III	1C	291
Psoriasis	ECP	Disseminated pustular	III	2B	293
	Adsorptive cytapheeresis	Disseminated pustular	III	2C	
	TPE	Disseminated pustular	IV	2C	
Red cell alloimmunization, prevention and treatment	RBC exchange	Exposure to RhD+ RBCs	III	2C	295
	TPE	Pregnancy, GA <20 wks	III	2C	
Scleroderma (systemic sclerosis)	TPE		III	2C	297
	ECP		III	2A	
Sepsis with multiorgan failure	TPE		III	2B	299
Sickle cell disease, acute	RBC exchange	Acute stroke	I	1C	301
	RBC exchange	Acute chest syndrome, severe	II	1C	
	RBC exchange	Other complications	III	2C	
Sickle cell disease, non-acute	RBC exchange	Stroke prophylaxis	I	1A	303
	RBC exchange	Pregnancy	II	2B	
	RBC exchange	Recurrent vaso-occlusive pain crisis	II	2B	
	RBC exchange	Preoperative management	III	2A	
Steroid-responsive encephalopathy associated with autoimmune thyroiditis (Hashimoto's encephalopathy)	TPE		II	2C	305
Stiff-person syndrome	TPE		III	2C	307
Sudden sensorineural hearing loss	LA/Rheopheresis/TPE		III	2A	309

Disease	TA modality	Indication	Category	Grade	Page
Systemic lupus erythematosus (SLE)	TPE	Severe complications	II	2C	311
Thrombocytosis	Thrombocytapheresis	Symptomatic	II	2C	313
	Thrombocytapheresis	Prophylactic or secondary	III	2C	
Thrombotic microangiopathy, coagulation mediated	TPE	THBD, DGKE, and PLG mutations	III	2C	315
Thrombotic microangiopathy, complement mediated	TPE	Factor H autoantibody	I	2C	317
	TPE	Complement factor gene mutations	III	2C	
Thrombotic microangiopathy, drug associated	TPE	Ticlopidine	I	2B	319
	TPE	Clopidogrel	III	2B	
	TPE	Gemcitabine/Quinine	IV	2C	
Thrombotic microangiopathy, infection associated	TPE/IA	STEC-HUS, severe	III	2C	321
	TPE	pHUS	III	2C	
Thrombotic microangiopathy, thrombotic thrombocytopenic purpura (TTP)	TPE		I	1A	323
Thrombotic microangiopathy, transplantation associated	TPE		III	2C	325
Thyroid storm	TPE		II	2C	327
Toxic epidermal necrolysis (TEN)	TPE	Refractory	III	2B	329
Transplantation, cardiac	ECP	Cellular/recurrent rejection	II	1B	331
	ECP	Rejection prophylaxis	II	2A	
	TPE	Desensitization	II	1C	
	TPE	Antibody-mediated rejection	III	2C	
Transplantation, hematopoietic stem cell, ABO incompatible (ABOi)	TPE	Major ABOi HPC(M)	II	1B	333
	TPE	Major ABOi HPC(A)	II	2B	
	RBC Exchange	Minor ABOi HPC(A)	III	2C	
	TPE	Major/Minor ABOi w/ pure RBC aplasia	III	2C	
Transplantation, hematopoietic stem cell, HLA desensitization	TPE		III	2C	335
Transplantation, liver	TPE	Desensitization, ABOi living donor	I	1C	337
	TPE	Desensitization, ABOi deceased donor/ Antibody-mediated rejection	III	2C	
	ECP	Desensitization, ABOi	III	2C	
	ECP	Acute rejection/Immune suppression withdrawal	III	2B	

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Disease	TA modality	Indication	Category	Grade	Page
Transplantation, lung	ECP	Bronchiolitis obliterans syndrome	II	1C	339
	TPE	Antibody-mediated rejection/desensitization	III	2C	
Transplantation, renal, ABO compatible	TPE/IA	Antibody-mediated rejection	I	1B	341
	TPE/IA	Desensitization, living donor	I	1B	
	TPE/IA	Desensitization, deceased donor	III	2C	
Transplantation, renal, ABO incompatible	TPE/IA	Desensitization, living donor	I	1B	343
	TPE/IA	Antibody-mediated rejection	II	1B	
Vasculitis, ANCA-associated (AAV)	TPE	MPA/GPA/RLV: RPGN, Cr ≥ 5.7	I	1A	345
	TPE	MPA/GPA/RLV: RPGN, Cr < 5.7	III	2C	
	TPE	MPA/GPA/RLV: DAH	I	1C	
	TPE	EGPA	III	2C	
Vasculitis, IgA (Henoch-Schönlein purpura)	TPE	Crescentic RPGN	III	2C	347
	TPE	Severe extrarenal manifestations	III	2C	
Vasculitis, other	TPE	Hepatitis B polyarteritis nodosa	II	2C	349
	TPE	Idiopathic polyarteritis nodosa	IV	1B	
	Adsorptive cytapheeresis	Behcet's disease	II	1C	
	TPE	Behcet's disease	III	2C	
Voltage-gated potassium channel (VGKC) antibody-related diseases	TPE/IA		II	1B	351
Wilson disease, fulminant	TPE		I	1C	353