Evidence and Decision Making in Apheresis Medicine

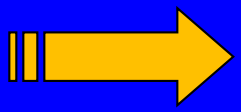
Robert Weinstein, MD

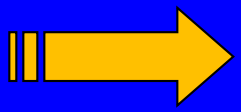
Past-President, World Apheresis Association
Past-President, American Society for Apheresis
Former Editor-in-Chief, Journal of Clinical Apheresis
Professor of Medicine & Pathology
University of Massachusetts Medical School
Worcester, Massachusetts USA

RW

Dr. Weinstein has no conflicts, financial or otherwise, to disclose.

Rationale for Apheresis Therapy

blood substance  clinical disorder

remove substance  improve disorder

The "Harvard Death"

No patient should die without…

circa 1960: …being restored to normal fluid and electrolyte status

circa 1970: …a trial of corticosteroids

circa 1980: …a course of plasma exchange

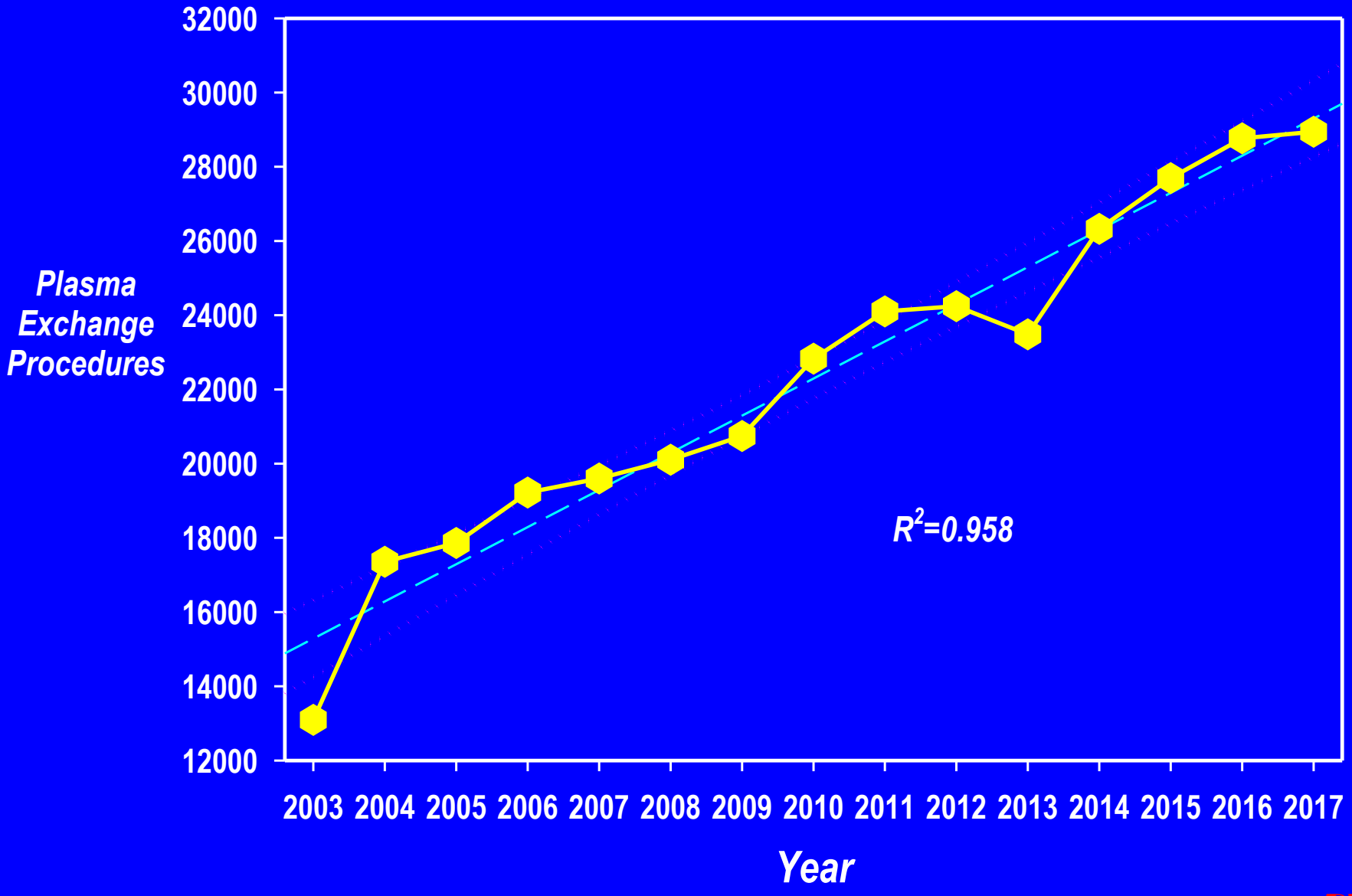
The Safety, Efficacy, and Cost Effectiveness of Therapeutic Apheresis (Office of Technology Assessment)

- A last resort in a wide range of diseases.
- Very few high quality studies document efficacy in actually improving health.
- Effective acute therapy in a few obscure diseases.
- Convincing proof of clinical efficacy lacking in most diseases in which apheresis is used.
- Optimal role and treatment parameters unknown.

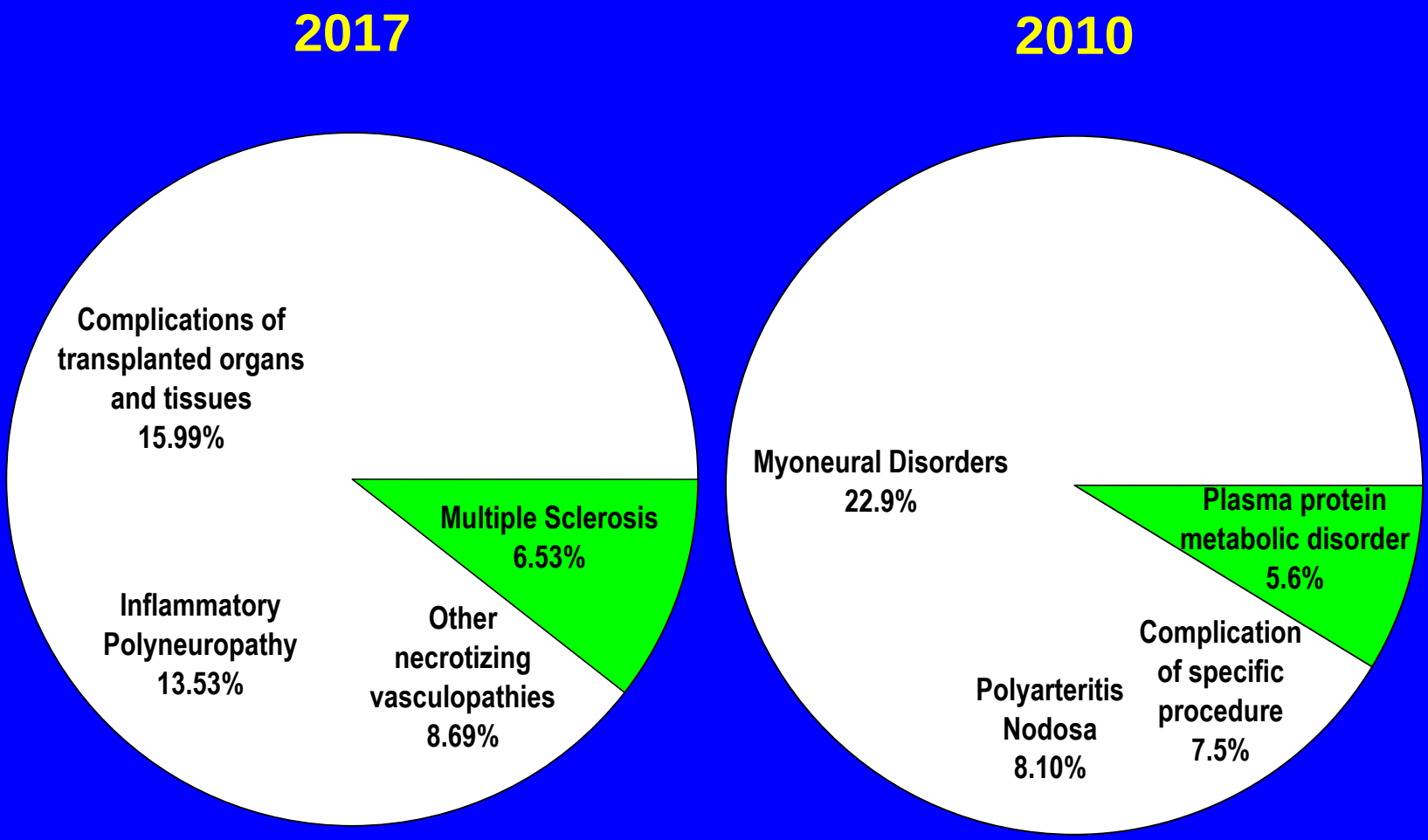
adapted from CTA-HCS-23, July 1983

RW

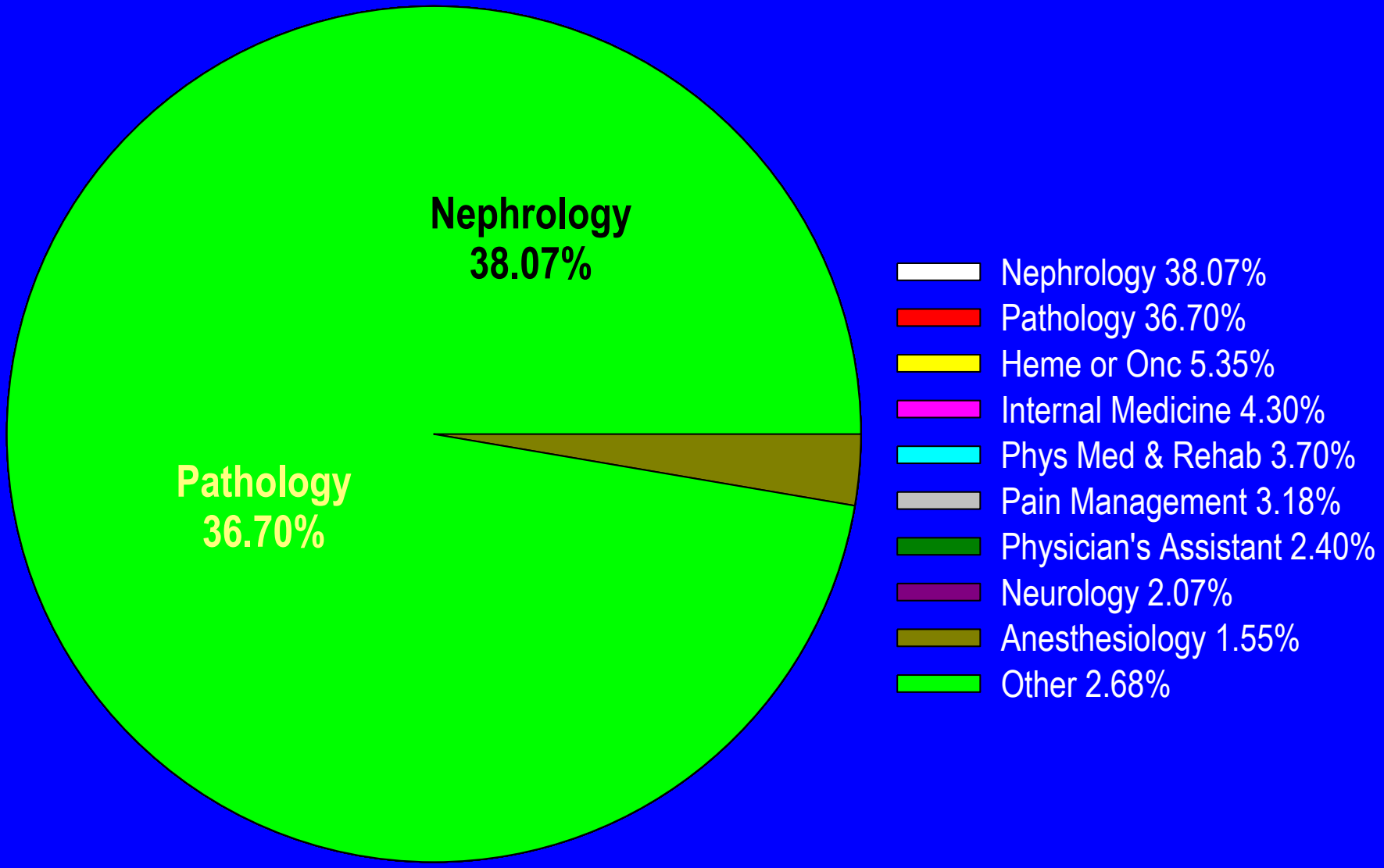
Plasma Exchanges Charged to US Medicare 2003-2017

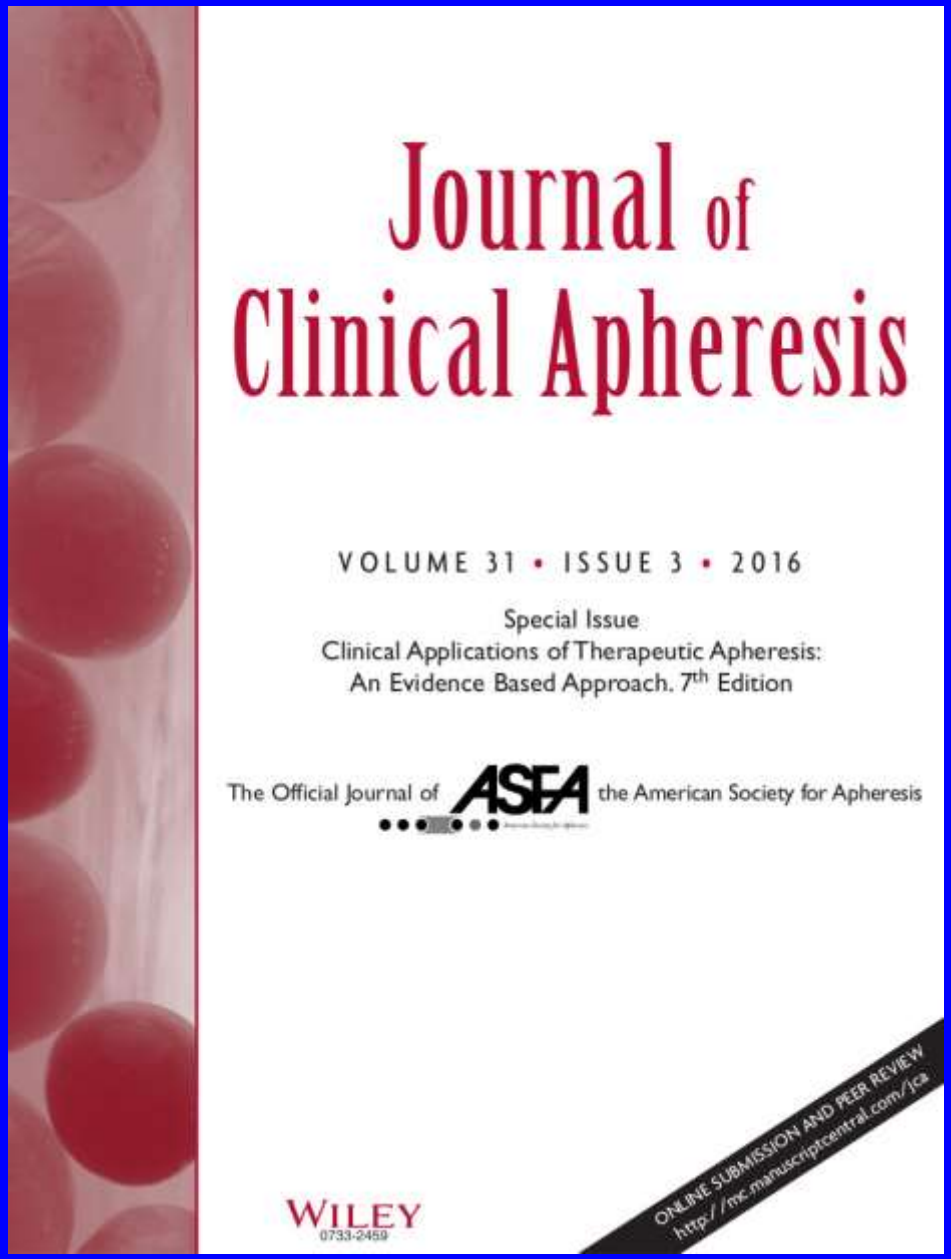


Leading Indications for Plasma Exchange in the United States



US Specialties Performing Therapeutic Plasma Exchange 2017




Journal of
Clinical Apheresis
VOLUME 31 • ISSUE 3 • 2016
Special Issue
Clinical Applications of Therapeutic Apheresis:
An Evidence Based Approach. 7th Edition
The Official Journal of ASFA the American Society for Apheresis
WILEY
0733-2459
ONLINE SUBMISSION AND PEER REVIEW
http://mc.manuscriptcentral.com/jca

2010 Revised ASFA Indication Categories (*with examples*)

Category I	First-line therapy: primary stand-alone treatment or in conjunction with other modes of treatment. *Acute Guillain-Barré Syndrome; Myasthenia Gravis*
Category II	Second-line therapy: stand-alone treatment or in conjunction with other modes of treatment. *Photopheresis for chronic GVHD after corticosteroid failure*
Category III	Optimum role of apheresis therapy not established. Decision making should be individualized. *DCM; Sepsis with Multiorgan Failure*
Category IV	Published evidence indicates apheresis to be ineffective or harmful. IRB approval is desirable. *Plasma Exchange for Active Rheumatoid Arthritis*

adapted from: Szczepiorkowski ZM et al. J Clin Apheresis 2010;25:83-177

Definition of the Quality of Evidence: ACCP Modification of GRADE

Evidence Quality	Grade	Definition
High	A	Confidence in recommendation unlikely to change with further research.
Moderate	B	Confidence in recommendation likely to be affected, and possibly changed, by further research.
Low	C	Confidence in recommendation very likely to be affected, and changed, by, further research.

based on *Guyatt GH et al. BMJ 2008;336:924-6*
Guyatt GH et al. Chest 2008;133:123S-131S
Guyatt G et al. Chest 2006;129:174-81

Modified GRADE System for Recommendations for Clinical Practice

Grade of Recommendation	Implications for Decision-making	
	For Patient	**For Clinician**
Strong (Grade 1) ***"We recommend"***	Most patients w*ould want* recommended intervention under similar circumstances	Most patients *should receive* recommended intervention under these circumstances
Weak (Grade 2) ***"We suggest"***	Most patients would want the recommended intervention under similar circumstances, *but many might not*	*Individualize approach* to helping patients decide regarding recommended intervention. *Take patient's values and preferences into account.*

adapted from Guyatt GH et al. Chest 2008;133:123S-131S

Fact Sheets: the Seventh ASFA Guidelines

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

Incidence: 8.5/1000,000/yr	**Indication**	**Procedure**	**Recommendation**	**Category**
	Dialysis dependence[a]	TPE	Grade 1A	I
	DAH	TPE	Grade 1C	I
	Dialysis independence	TPE	Grade 2C	III
No. of reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	8 (296)	1 (26)	22 (347)	NA

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

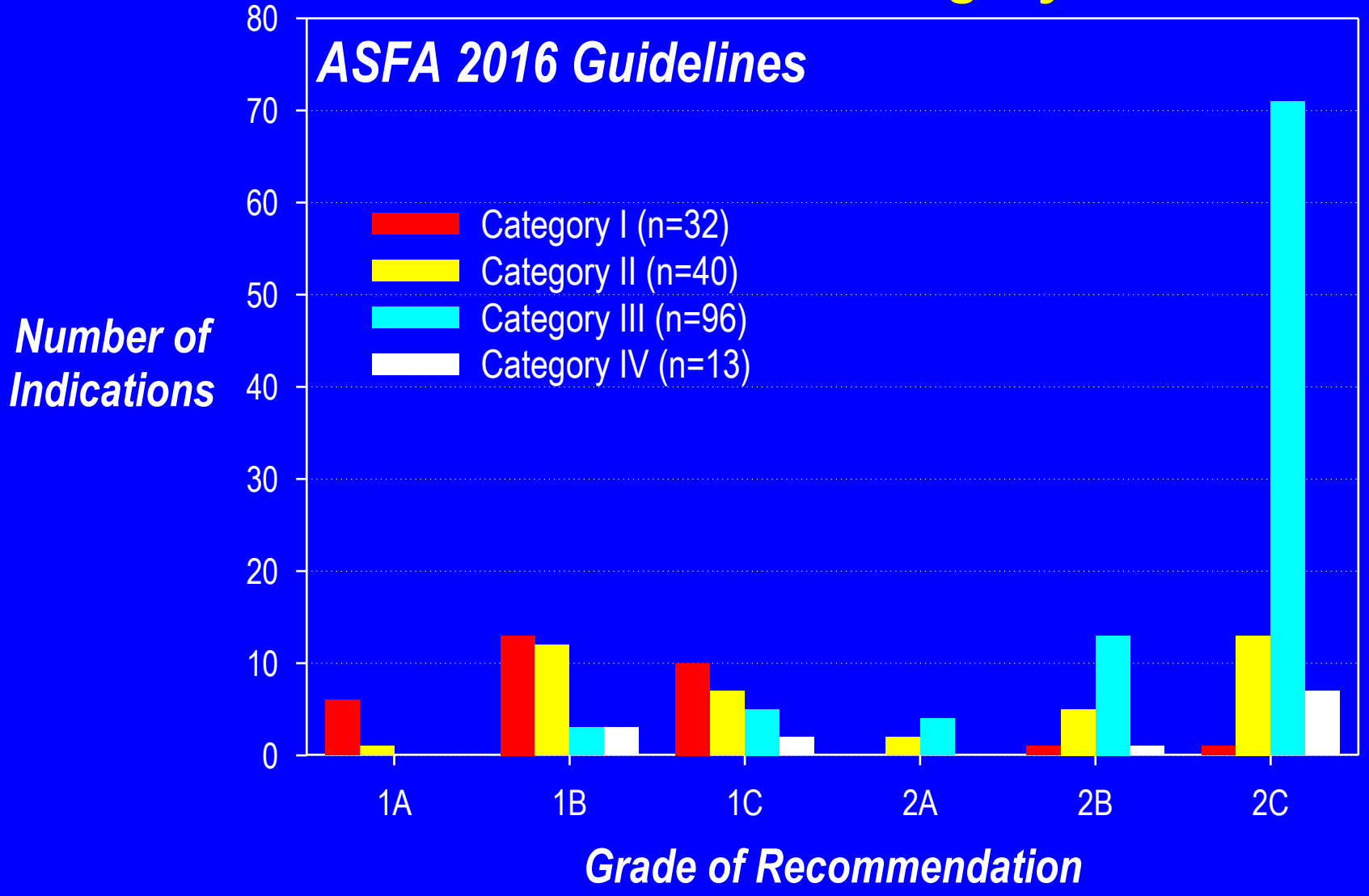
ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE (GOODPASTURE'S SYNDROME)

Incidence: 1/1000,000/yr	**Indication**	**Procedure**	**Recommendation**	**Category**
	Dialysis dependence[a], no DAH	TPE	Grade 2B	III
	DAH	TPE	Grade 1C	I
	Dialysis independence	TPE	Grade 1B	I
No. of reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	1(17)	0	19 (468)	21

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

adapted from Schwartz J et al. J Clin Apher 2016

Grade of Recommendation vs. Indication Category



adapted from Schwartz J et al. J Clin Apher 2016

McLeod's Criteria for Likelihood of Benefit of Apheresis Therapy

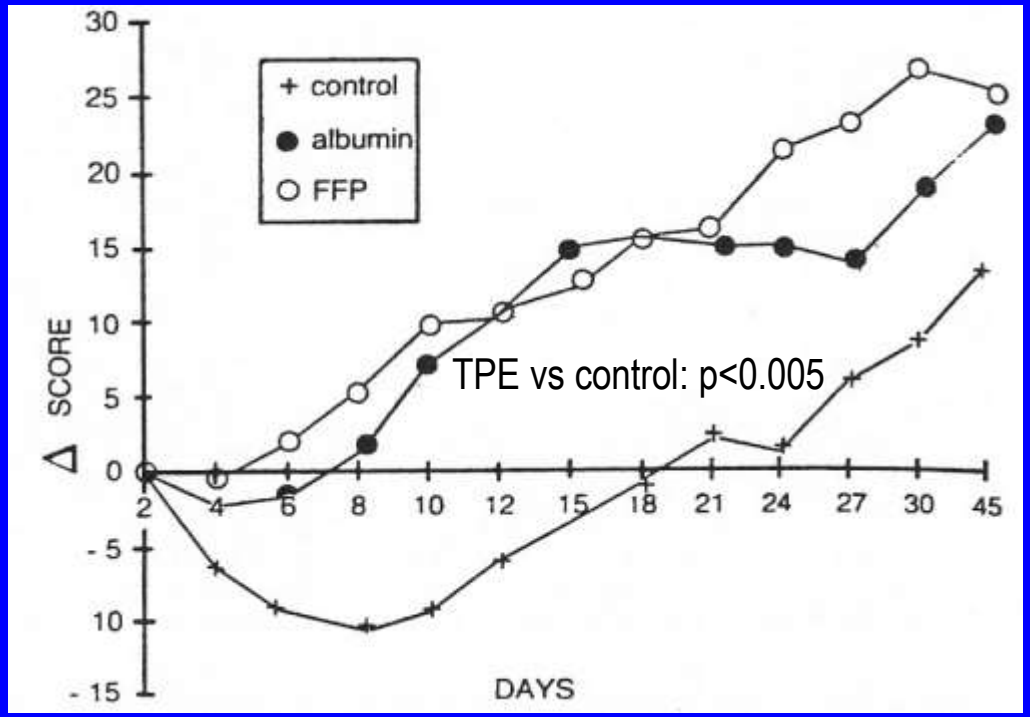
"Plausible Pathogenesis"	A secure understanding of the disease process suggests a clear rationale for apheresis therapy.
"Better Blood"	The abnormality that makes apheresis plausible is meaningfully corrected by apheresis therapy.
"Perkier Patients"	There is strong evidence that apheresis therapy confers clinical benefit that is meaningful (not only statistically significant).

McLeod BC J Clin Apheresis 2002;17:124-132

Acute Guillain-Barré Syndrome

- Idiopathic inflammatory demyelinating polyneuropathy
  - Ascending, progressive muscle weakness, areflexia
  - Association with antecedent Campylobacter jejuni infection (60%)
  - Annual incidence: 1 to 4 per 100,000 worldwide
- Clinical course
  - Assisted ventilation: 10-25%
  - Death: 4-15%
  - Persistent mild neurological deficits: 67%
  - Persistent disabling neurological deficits: 5-15%
- Autoimmune disorder
  - Complement fixing IgM anti-peripheral nerve myelin antibodies
  - Anti-GM_1 antibodies (severe axonal involvement)
  - Anti-GQ_{1b} antibodies (Fisher's syndrome: ataxia, ophtalmoplegia, areflexia)

Rapid Response of Acute Guillain-Barré Syndrome to Plasma Exchange



109 TPE vs 111 controls
92% ≥ grade 3

	TPE	Control	*p*
Time to grade 2 (days*)	70	111	<0.001
Hospital stay (days*)	28	45	<0.001
Full strength by 1 year	71%	52%	0.007

*median

from the French Cooperative Group Trial:
Ann Neurol 1987;22:753-761
Ann Neurol 1992;32:94-97

“McLeod’s Criteria” Applied to Conditions Treated by Apheresis

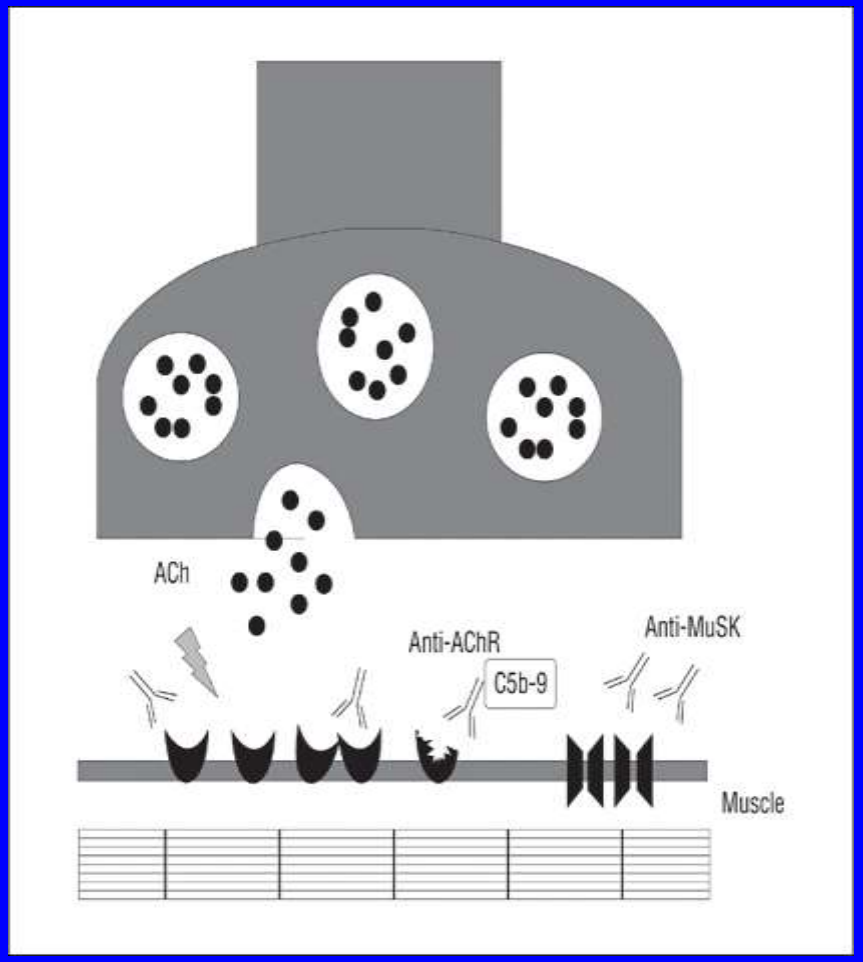
Condition	Plausible Pathogenesis	Better Blood	Perkier Patients	Recommended Regimen
Acute GBS Cat I Grade 1A	Anti-myelin Antibody	Antibody↓with TPE	Randomized trials	Based on clinical trials

adapted from McLeod BC J Clin Apheresis 2002;17:124-132

Myasthenia Gravis

An Autoimmune Disorder of the Neuromuscular Junction

- Autoantibody mediated
  - Acetylcholine receptor (AChR) antibodies
  - Anti-muscle-specific receptor tyrosine kinase
- Thymoma in 10-15%, esp. ♂ >40 yrs
- Variable weakness of voluntary muscles
  - Accentuated by repetitive motion
  - Alleviated by rest
  - Bulbar, extremity, trunk muscles
- Treatment
  - Acetylcholinesterase inhibitors
  - Immunosuppression
- Major role of TPE
  - Pre-op preparation for thymectomy
  - Acute exacerbations



Cartoon: Lehmann, H. C. et al. Arch Neurol 2006;63:1066-1071.

Compilation of Level II Evidence Regarding TPE for Myasthenia Gravis

Seven open studies of at least 15 patients							
Authors	**Year**	**patients**	**Pred**	**Immunosuppressor**	**TPE/pt**	**L exchanged**	**Effect (%)**
Behan	1979	21	Y	Y	?	16-32	100
Dau	1981	60	48	48	9-33		73
Olarte	1981	21	13	12	2-10		81
Perlo	1981	17	?	?	3-5		65
Fornasari	1985	33	11	11	4-8		61
Antozzi	1991	70	?	?	2		70
Chiu	2000	94	?	?	4-5		85
Total		316					76.4

"No adequate randomised controlled trials have been performed to determine whether plasma exchange improves the short- or longterm outcome for myasthenia gravis. However, many case series studies report short-term benefit from plasma exchange in myasthenia gravis, especially in myasthenic crisis. Further research is need to compare plasma exchange with alternative short-term treatments for myasthenic crisis and to determine the value of long-term plasma exchange for treating myasthenia gravis."

Gajdos P, Chevret S, Toyka K. Plasma exchange for myasthenia gravis. *Cochrane Database of Systematic Reviews* 2002, Issue 4. Art. No.:CD002275. DOI: 10.1002/14651858.CD002275.

Controlled Trials of TPE in Myasthenia Gravis

Authors	Study Design	Population	Intervention	Outcome Measures	Results
Goti P et al. Thorax 1995;50:1080-6.	Non-randomized, baseline to treatment	9 patients with grade IIb myasthenia	Baseline of treatment with pyridostigmine compared to treatment with TPE	• Pulmonary volumes • Inspiratory and expiratory muscle force • Respiratory muscle strength, Ventilatory pattern ○ Inspiratory time ○ Expiratory time ○ Total time of respiratory cycle ○ Tidal volume	Decrease in FRC and RV Increase in FEV1, MIP Increase in MEP TPE vs pyridostigmine ($p<0.05$).
Nagayasu T et al. Jpn J Thorac Cardiovasc Surg 2005;53:2-7.	Retrospective, cohort study	51 patients with MG treated with trans-sternal thymectomy	19 patients: 1 TPE prior to thymectomy. 32 patients: thymectomy alone.	• Incidence of MG crisis • Pharmacologic remission and improvement rate, evaluated by graded scale	<u>TPE vs CONTROL</u> •Crisis within 1 year post-op: 5.3% vs 28.1% ($p=0.049$); •Crisis within 30 days post-op: 0 vs 15.6% ($p=0.0724$). •Improvement rate: 100% vs 81.3% ($p=0.0466$). •Complete remission (5-7 yrs): 79% vs 50% ($p=0.0427$) .

adapted from Cortese I et al. Neurology 2011;76:294-300

RW

“McLeod’s Criteria” Applied to Conditions Treated by Apheresis

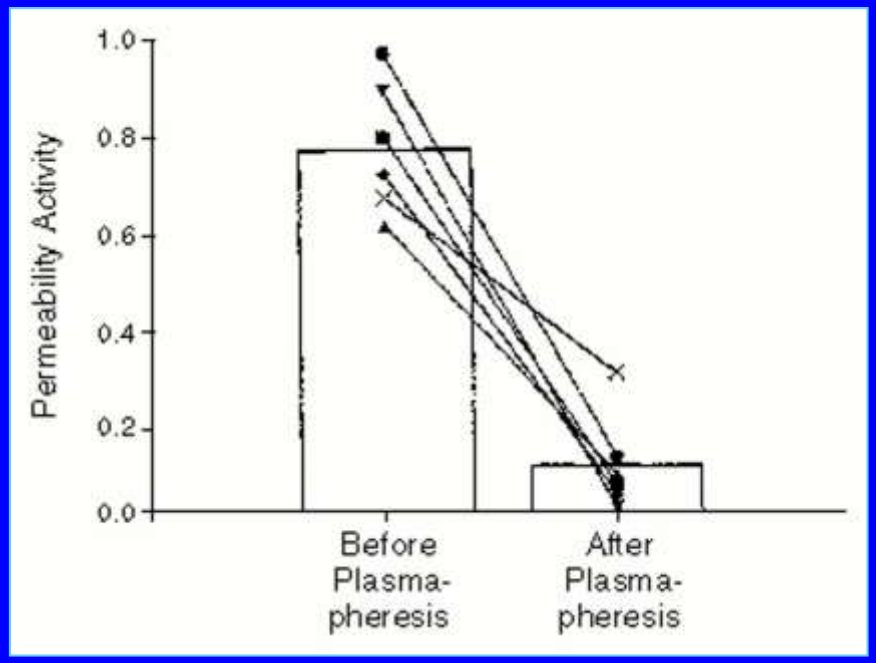
Condition	Plausible Pathogenesis	Better Blood	Perkier Patients	Recommended Regimen
Acute GBS Cat I Grade 1A	Anti-myelin Antibody	Antibody↓with TPE	Randomized trials	Based on clinical trials
Myasthenia Gravis Cat I Grade 1B	ACh-receptor Antibody	↓ ACh receptor Antibody	Strong but anecdotal	? optimal regimen

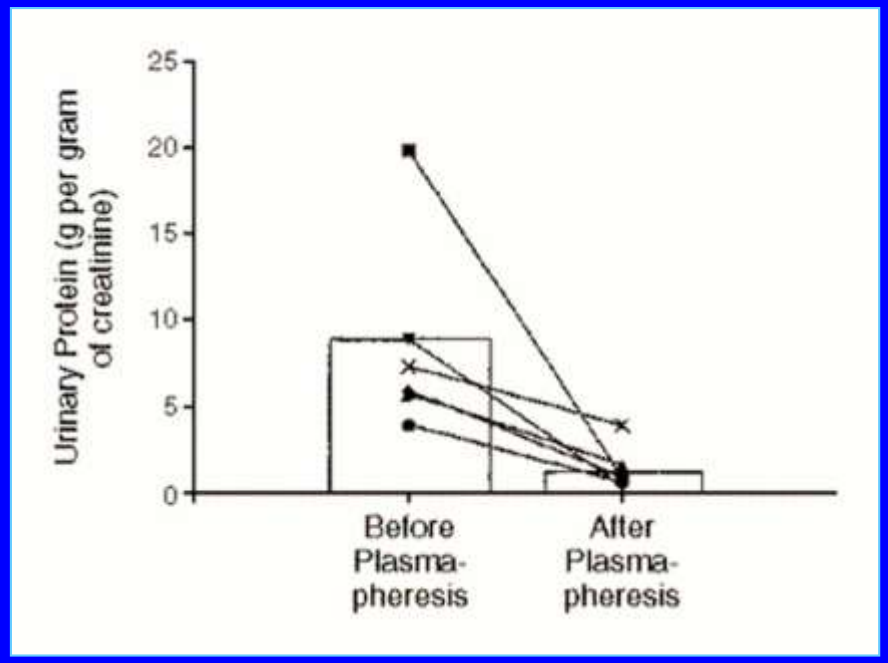
adapted from McLeod BC J Clin Apheresis 2002;17:124-132

Focal Segmental Glomerulosclerosis

- 15-20% of idiopathic nephrotic syndrome
- 30% recurrence post-transplant
  - 50% graft loss within 2 years
  - Higher risk with presentation before age 20
  - Up to 80% recurrence in subsequent graft
- Circulating permeability factor? *(suPAR?)*
  - Disease transferable to animals with patient plasma
  - 30-50 kDa protein
  - Sensitive to heat, proteolysis, $[NH_4]_2SO_4$
- Treatment: controversial?
  - Corticosteroids, cytotoxic drugs
  - ACE inhibitors
  - Apheresis approach to circulating permeability factor?

Permeability Factor and Proteinuria in Focal Segmental Glomerulosclerosis





from Savin VJ et al. N Engl J Med 1996;334:878-83

Plasma Exchange in Recurrent FSGS After Kidney Transplant

Patient number	FSGS diagnosis post transplant	Recurrence days post transplant	Number of PE Procedures	Urinary protein (U.P.) (g/24 h)		Percentage decrease in U.P.	Post PE follow-up U.P.
				Pre 1st TPE	Post TPE		
1	Clinical	3	6	4.0	0.3	92	0.3 g/24 h 2 weeks
2	Clinical	3	10	40.0	0.2	99	0.2 g/24 h 2 months
3	Biopsy	5	8	11.0	6.0	45	Not available
4	Clinical	7	5	5.9	0.4	93	0.2 g/24 h 1 year
5	Clinical	7	11	4.0	0.3	92	0.3/24 h 3 months
6	Clinical	7	5	4.2	0.6	85	Negative 1.5 years
7	Biopsy	11	5	8.0	2.4	70	0.3 g/24 h 11 months
8	Biopsy	26	5	4.0	3.7	8	0.2 g/dl 2.5 year
9	Biopsy	66	5	6.1	0.2	97	Negative 9 months
10	Biopsy	52	11	11.0	6.0	45	0.8 g/24 h 11 months
11	Biopsy	> 700 (2 years)	6	3.0	1.5	50	0.4 g/24 h 5.5 year

All were on immunosuppressive drugs.

Shariatmadar S and Noto TA. J Clin Apheresis 2002;17:78-83

10 High-Risk Patients with FSGS who Received TPE Peri-Transplantation

Patient	Follow-up (days)	Induction therapy*	Current immuno-suppression**	Recurrence	Proteinuria (g/day)	Rejection	Serum creatinine (mg/dL)
1	1258	T	T/M/P	N	0.30	N	1.0
2	980	B	T/M/P	N	0.19	N	1.1
3	959	B	T/M/P	N	0.39	Y	1.8
4	749	T	T/I	Y	4.75	N	2.6
5	735	B	T/M/P	N	0.81	Y	1.3
6	699	T	R/I/P	N	0.39	N	2.0
7	644	B	T/M/P	N	0.33	N	1.5
8	962	B	T/I/P	Y	37.1	N	HD
9	238	T	T/M/P	Y	7.5	N	HD
10	287	T	T/M/P	N	0.59	N	0.9

*T = thymoglobulin; B = basiliximab.

**T = tacrolimus; M = mycophenolate mofetil; P = prednisone.

from Gohh et al. Am J Transplant 2005;5:2907-12

"McLeod's Criteria" Applied to Conditions Treated by Apheresis

Condition	Plausible Pathogenesis	Better Blood	Perkier Patients	Recommended Regimen
Acute GBS Cat I Grade 1A	Anti-myelin antibody	Antibody↓with TPE	Randomized trials	Based on clinical trials
Myasthenia Gravis Cat I Grade 1B, 1C	ACh-receptor Antibody	↓ ACh receptor Antibody	Strong but anecdotal	? optimal regimen
Focal Segmental Glomerular Sclerosis (recurrent post transplant) Cat I Grade 1B (2016)	Permeability factor (PF)	↓PF ↓Proteinuria	Largely anecdotal. Small numbers	Variable Not determined

McLeod's Criteria for Likelihood of Benefit of Apheresis Therapy

"Plausible Pathogenesis"	A secure understanding of the disease process suggests a clear rationale for apheresis therapy.
"Better Blood"	The abnormality that makes apheresis plausible is meaningfully corrected by apheresis therapy.
"Perkier Patients"	There is strong evidence that apheresis therapy confers clinical benefit that is meaningful (not only statistically significant).

McLeod BC J Clin Apheresis 2002;17:124-132

<u>Corollary Considerations</u>

- Is the problem potentially reversible with apheresis therapy?
- Is there a first-line or standard therapy?
  - Has it been tried?
  - Outcome?
- If apheresis to be tried, is the goal of a therapeutic trial defined?

Individualize Apheresis Decision Making for Patients with Rasmussen's Encephalitis

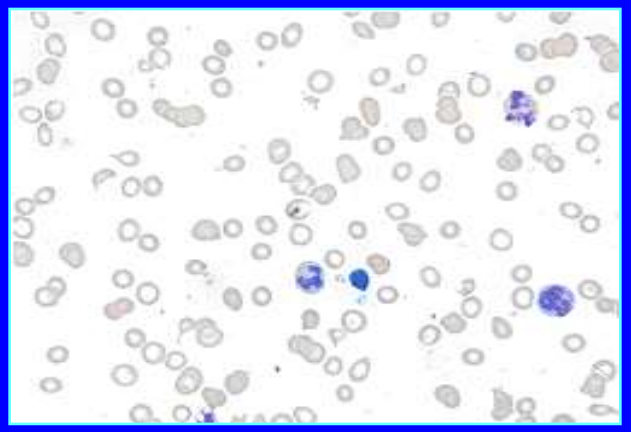
- 22 y/o ♀ with RE since age 8 yrs
  - Major partial seizures Q 15 min
  - Cognitive decline (7-8 y/o level)
  - Right hemiparesis (wheelchair)
  - Anti-GluR3 negative
- Therapies applied
  - Anticonvulsants – partial control
  - Surgery – transient↓ seizures
  - IVIG – no response
- Plasma exchange (since 5/2/2008)
  - Initially 3 TPE per week
  - Weekly since Sept 2008
  - Ambulatory
  - ↓↓ seizures
  - ↑ cognitive function

Maintained for many years with intermittent TPE

68 year old ♀ with CMML

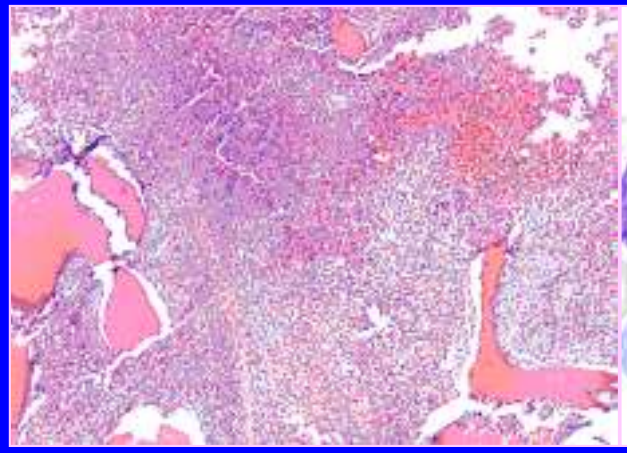
Peripheral Blood:

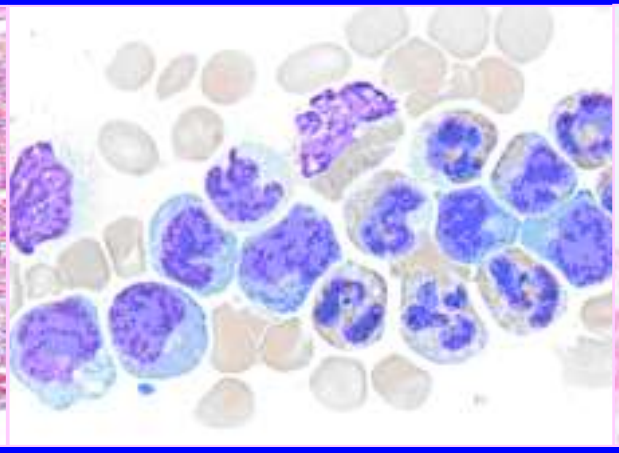
WBC	45,000/µL
HCT	31.8%
MCV	73.7 FL
PLT	3,000/µL
Mono	3,400/µL

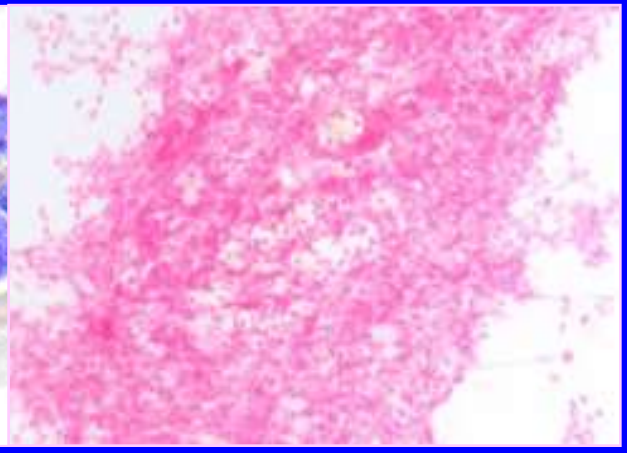


Bone Marrow:

Cellularity 95% Morphology dysplastic Megakaryocytes ↓↓↓ Iron: absent





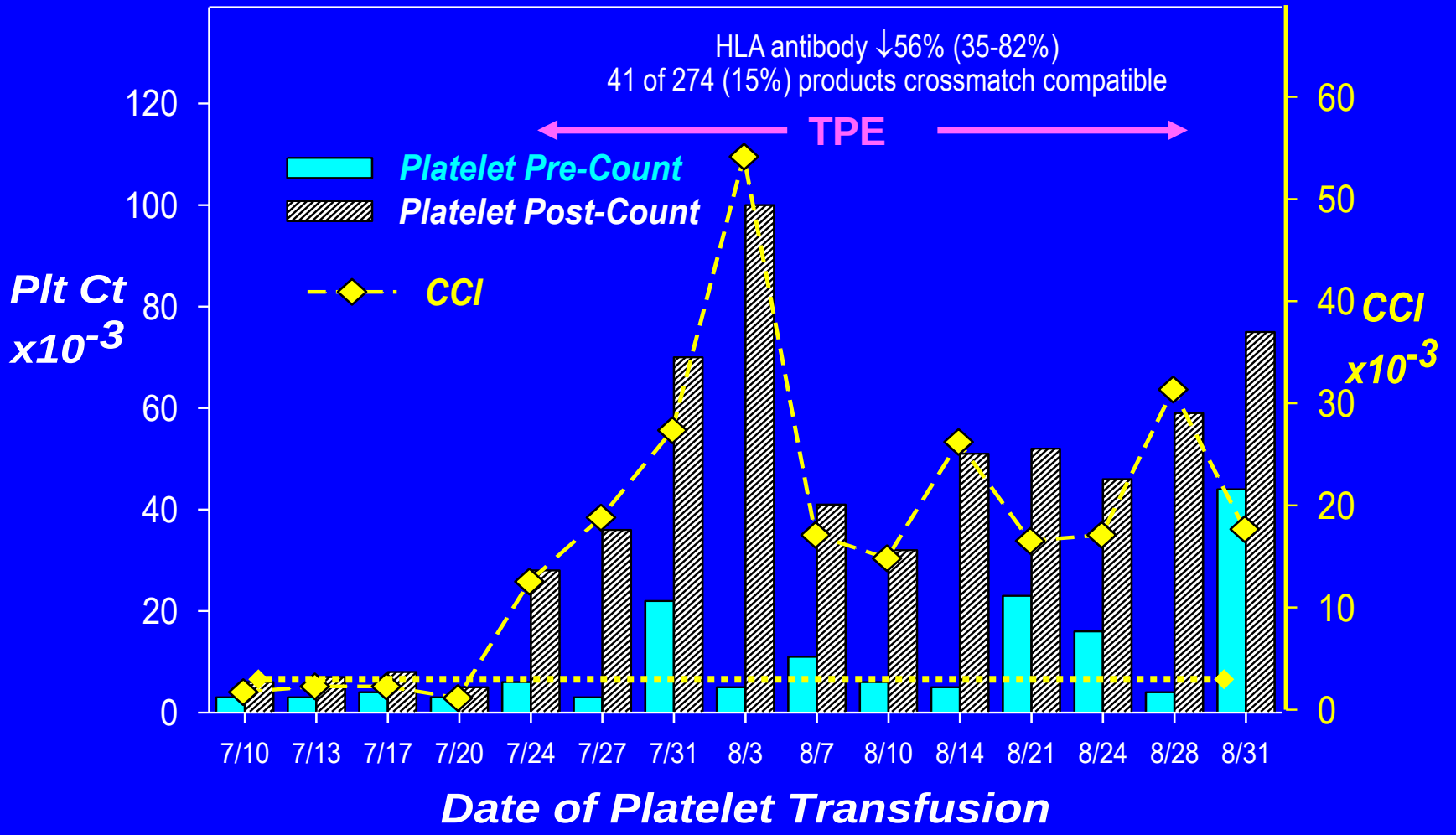


Severe Symptomatic Thrombocytopenia

- Clinical manifestations
  - Petechial rash & spontaneous ecchymoses
  - Severe, constant hematochezia
  - Retrotympanic bleeding → hearing loss
- Attempts to manage thrombocytopenia & hemorrhage
  - IVIG
  - Steroids
  - RBC transfusion
  - Platelet transfusion
- HLA phenotype: A23, A66, B7, B41
- > 40% PRA on HLA antibody screen
- HLA antibody specificities
  - Broad spectrum
  - Class I and II

  A2, A30, A31, A32, A33, A36, A68, A69
  B35, B45, B51, B52, B53, B57
  DR4, DR7, DQ7, DQ8
- Initial platelet crossmatching
  - 7 crossmatch panels
  - 2 of 117 (1.7%) apheresis platelet units compatible

Platelet Support of Patient PK



$$CCI = \frac{(\text{Post Tx PLT}) - (\text{Pre Tx PLT})}{\text{* \# of Platelets Transfused}} \times \text{BSA } (M^2)$$

*multiples of 10^{11}

Evidence Based Medicine: Caveats

"...integrat[e] individual clinical expertise with the best available external clinical evidence ..."

"Without clinical expertise, practice risks becoming tyrannized by evidence...[which may be] inapplicable to an individual patient."

"Without current best evidence, practice risks becoming rapidly out of date."

adapted from Sackett DL et al. BMJ 1996;312:71-2.

Using Available Tools for Clinical Decision Making in Apheresis Medicine

- Indication Categories – ASFA Fact Sheets
  - Where does apheresis fit into treatment scheme
  - Assessment of strength of published evidence
- McLeod's Criteria
  - Framework for taking stock of available data
  - Plausibility of achieving benefit with apheresis
- Corollary Considerations
  - Framework for incorporating clinical judgment
  - Formulation of specific therapeutic trial

Apheresis at the Bedside

$$\frac{\text{Evidence X Knowledge}}{\text{Individualized Judgment}} = \text{Rational Apheresis Decision Making}$$