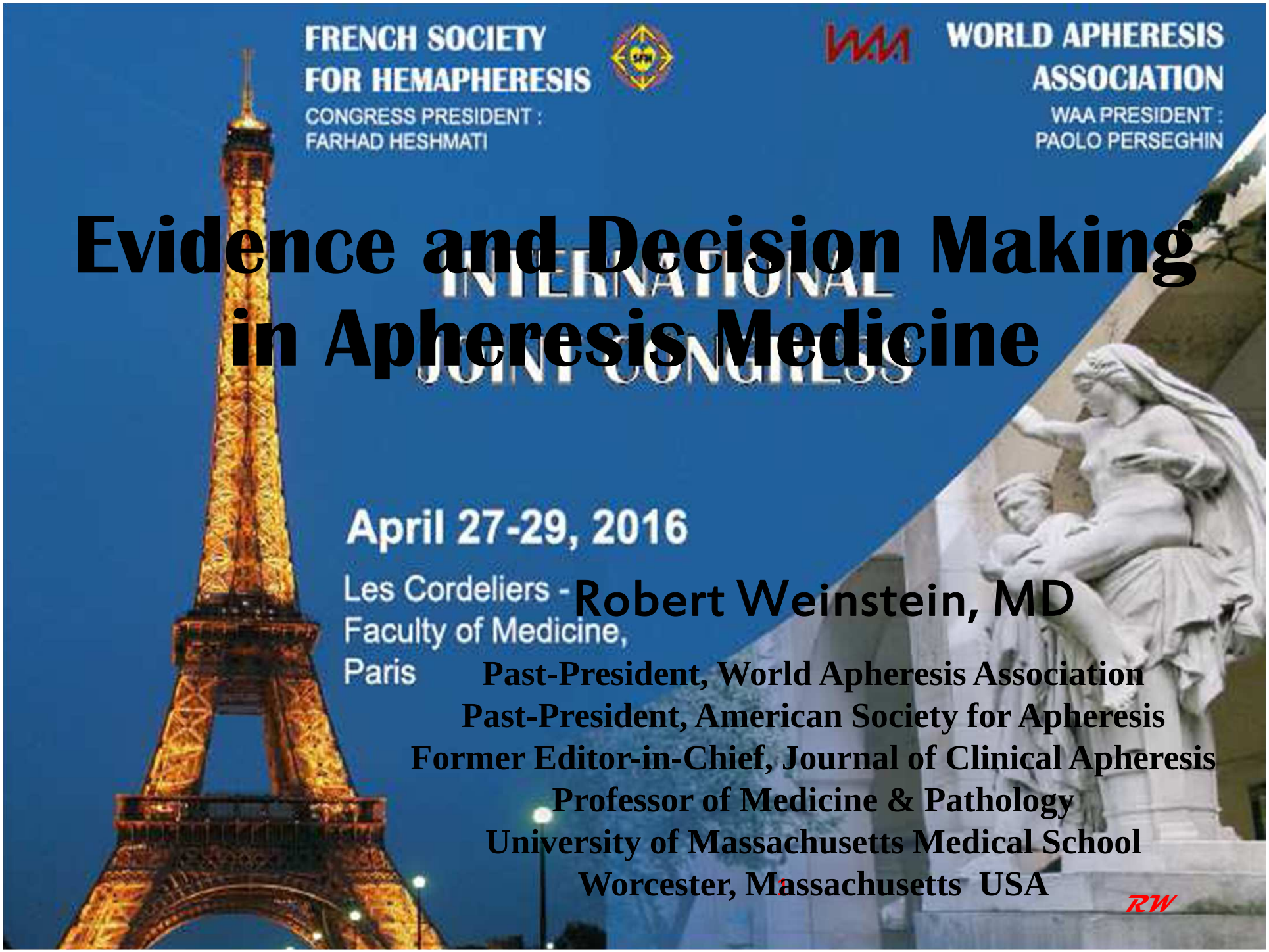

Evidence and Decision Making in Apheresis Medicine

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RW

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

Fact Sheet: the Sixth ASFA Guidelines

ACUTE INFLAMMATORY DEMYELINATING POLYNEUROPATHY (GUILLAIN-BARRÉ SYNDROME)

Incidence: 1-2/100,000/yr	**Condition**	**Procedure**	**Recommendation**	**Category**
		TPE	Grade 1A	I
	After IVIG*	TPE	Grade 2C	III

# of reported patients*: >300

	RCT	**CT**	**CS**	**CR**
	19 (1770)	0	9 (369)	10 (11)
After IVIG*	0	0	1 (46)	NA

*completed course of IVIG at 2 g/kg

GRAFT-VERSUS-HOST DISEASE

Incidence: After allogenic HSC transplant: 10-60% Grade II-IV acute GVHD; 6-80% moderate-severe chronic GVHD	**Condition**	**Procedure**	**Recommendation**	**Category**
	Skin (chronic)	ECP	Grade 1B	II
	Skin (acute)	ECP	Grade 1C	II
	Non-skin	ECP	Grade 2B	III

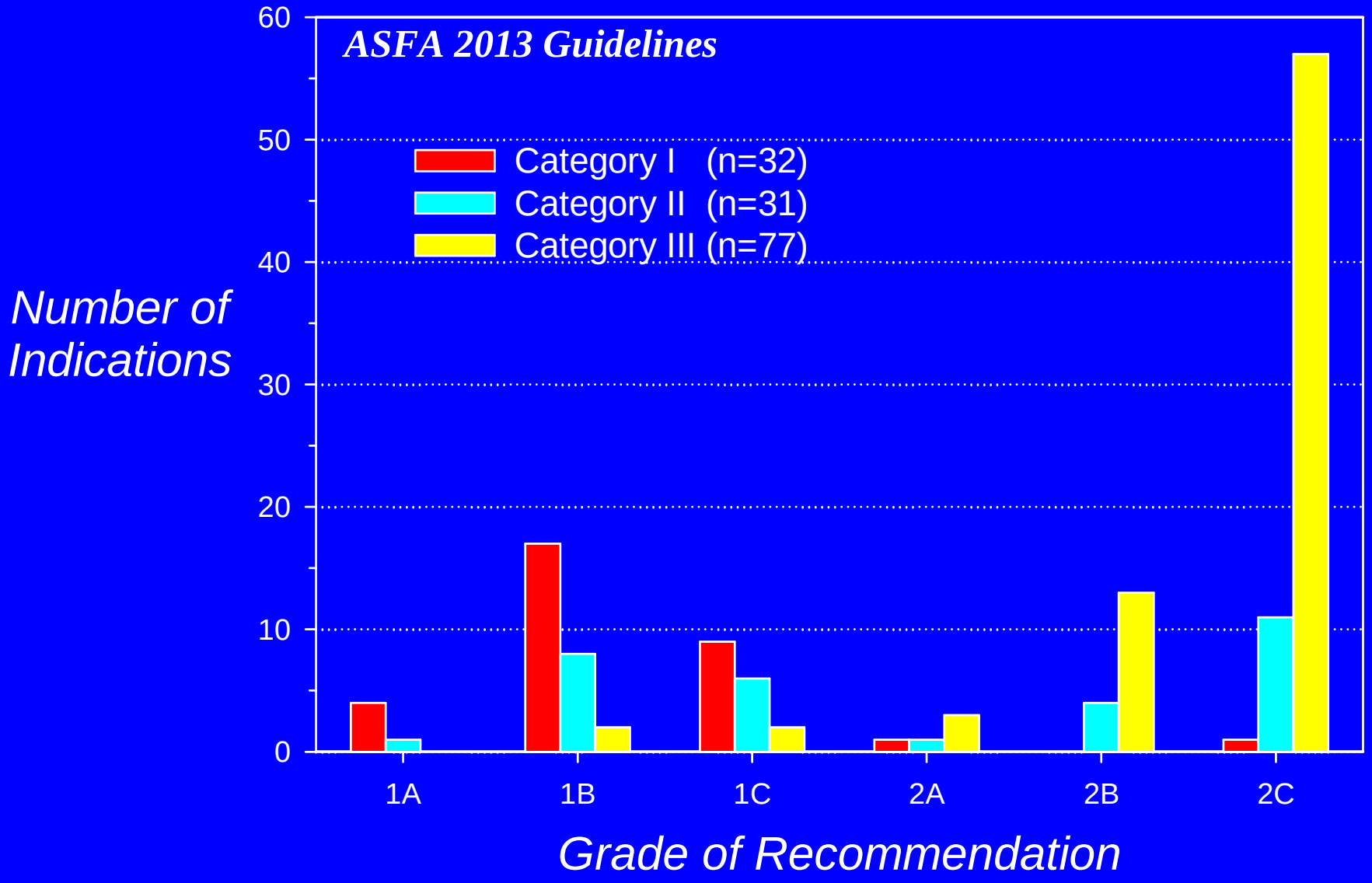
# of reported patients*: >300

	RCT	**CT**	**CS**	**CR**
Chronic skin	1 (95)	0	0	0
Acute/chronic skin and non-skin	0	2 (41)	44 (944)	9 (13)

GVHD = graft-versus-host disease

adapted from Schwartz J et al. J Clin Apher 2013

Grade of Recommendation vs. Indication Category



adapted from Schwartz J et al. J Clin Apher 2013

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

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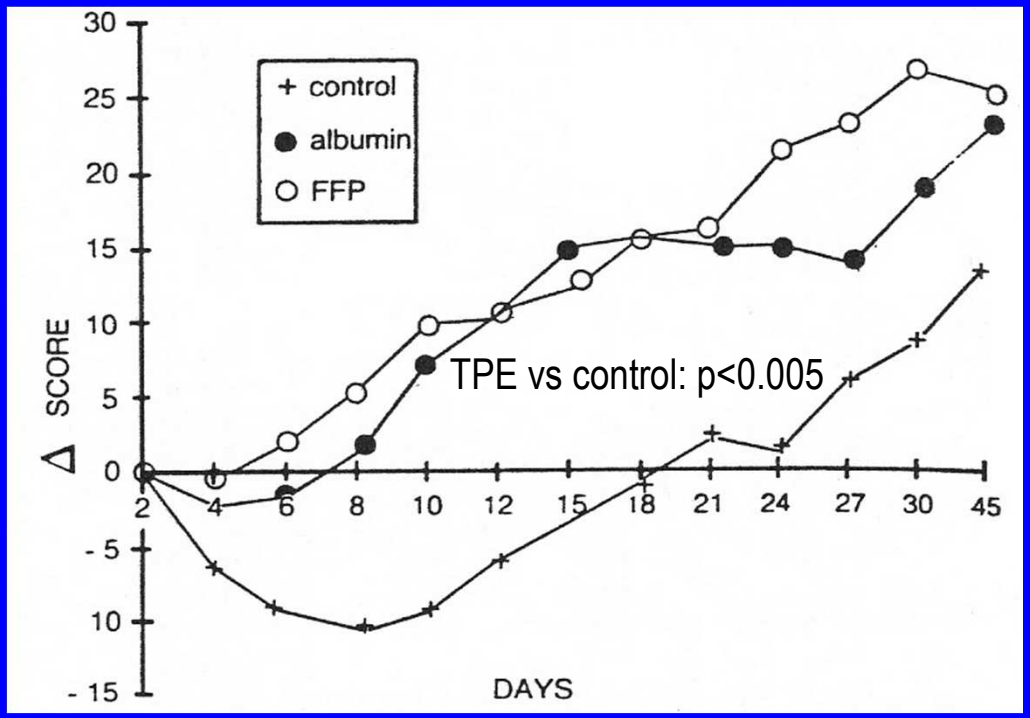
Acute Guillain-Barré Syndrome

- 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

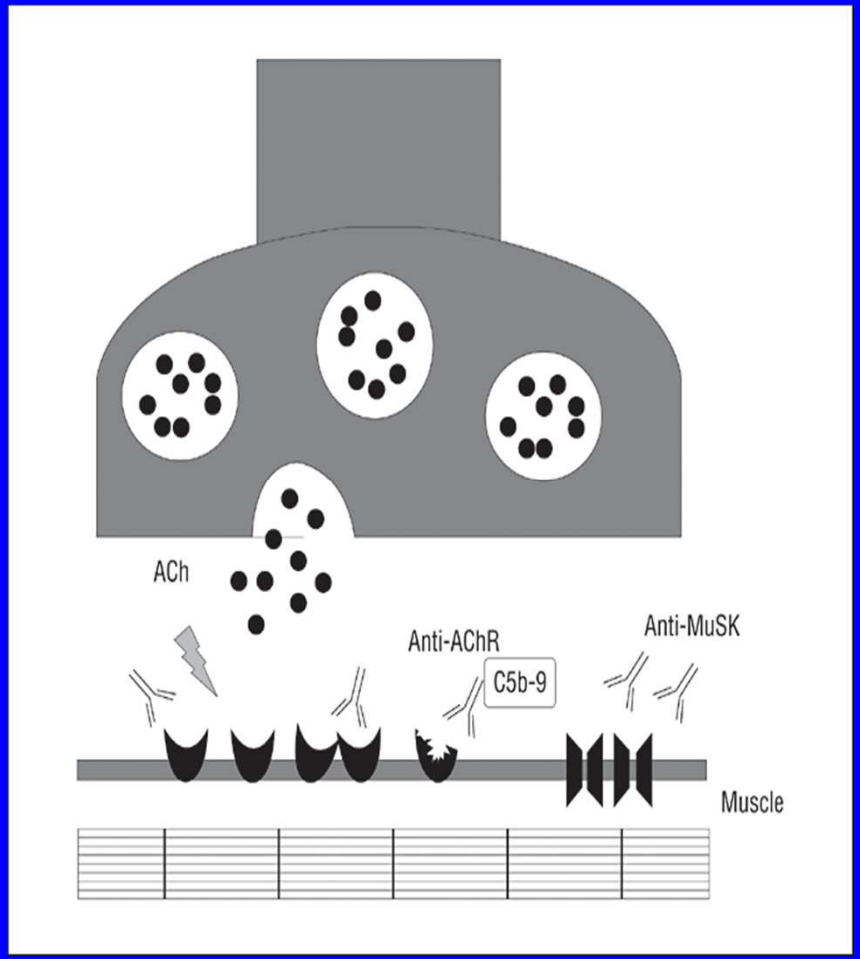
Condition	Plausible Pathogenesis	Better Blood	Perkier Patients	Recommended Regimen
Acute GBS Cat I Grade 1A	Anti-myelin Antibody	Antibody↓with TPE	Randomized trials	Based on clinical trials

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 o Inspiratory time o Expiratory time o Total time of respiratory cycle o 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

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"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

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Rasmussen's Encephalitis
(Epilepsia Partialis Continua)

- Intractable focal seizures
- Onset usually in childhood
- ?post-viral etiology
- Clinical picture
  - Anticonvulsant-refractory epilepsy
  - Progressive hemiparesis
  - Progressive unilateral cerebral atrophy
  - Progressive cognitive decline
- Treatment
  - Anticonvulsant medication
  - High-dose corticosteroids
  - Subtotal, functionally complete, hemispherectomy
  - IVIG, IFN, ?Rituximab

"A clinicopathologic report is made of three children suffering from a chronic illness, producing focal seizures and gradually producing severe damage to one cerebral hemisphere. The…lesion is a chronic focal encephalitis. The etiology is undetermined…"
Rasmussen T et al. Neurology 1958;8:435-45

adapted from Weinstein R J Clin Apheresis 2000;15:121-3

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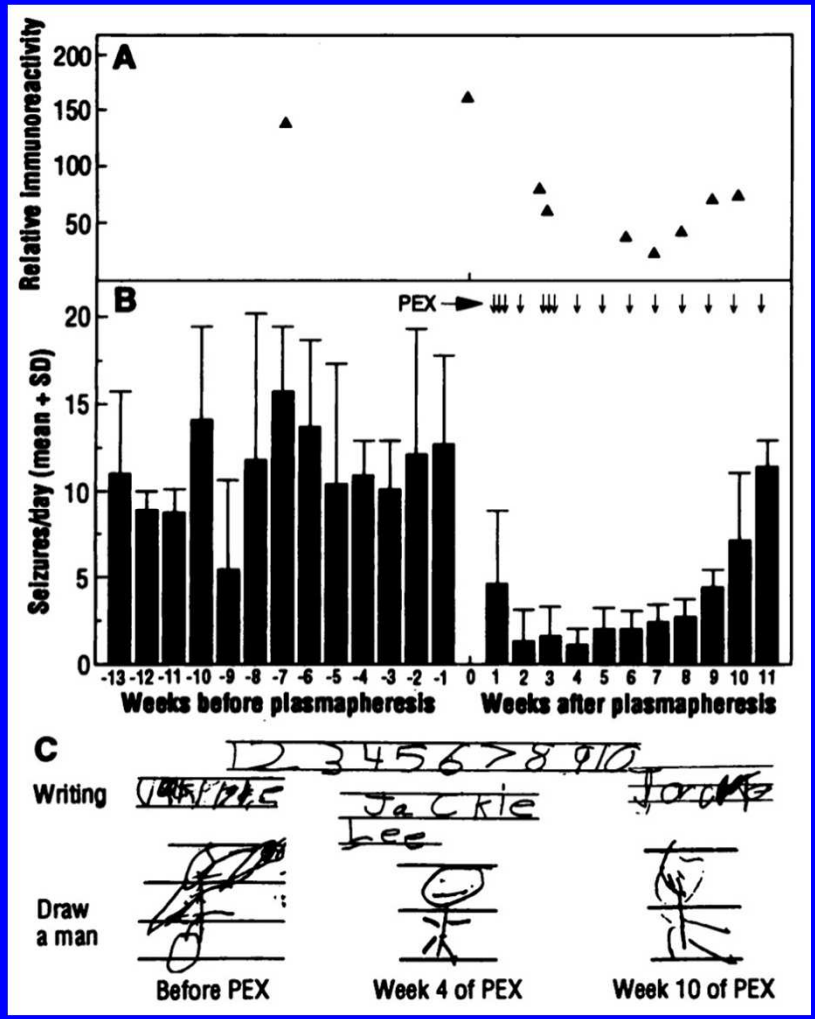
Is Rasmussen's Encephalitis an Autoimmune Disease Treatable with Plasma Exchange?

- Attempt to raise rabbit glutamate receptor antibodies
- Rabbits developed anti-GluR3
  - Recurrent seizures
  - Inflammatory histopathology
  - Localization to cortex
- Anti-GluR3 in patients' serum
  - 3 of 4 children with RE
  - ? correlated with disease activity
- 1 child treated with TPE
  - Single volume procedures
  - Improvement during 1st 7 weeks
    - Seizures ↓ 80%
    - Cognition, speech
    - hemiparesis
  - Subsequent relapse



adapted from Rogers SW et al. Science 1994;265:648-51

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

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Acute GBS Cat I Grade 1A	Anti-myelin antibody	Antibody↓with TPE	Randomized trials	Based on clinical trials
Myasthenia Gravis Cat I Grade 1A	ACh-receptor Antibody	↓ ACh receptor Antibody	Strong but anecdotal	? optimal regimen
Rasmussen's Encephalitis Cat III Grade 2C	?autoimmune inflammation	? ↓ GluR3 autoantibodies	Low-quality evidence	Not determined

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

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

Corollary Considerations

- 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

- 18 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

Now maintained with intermittent TPE

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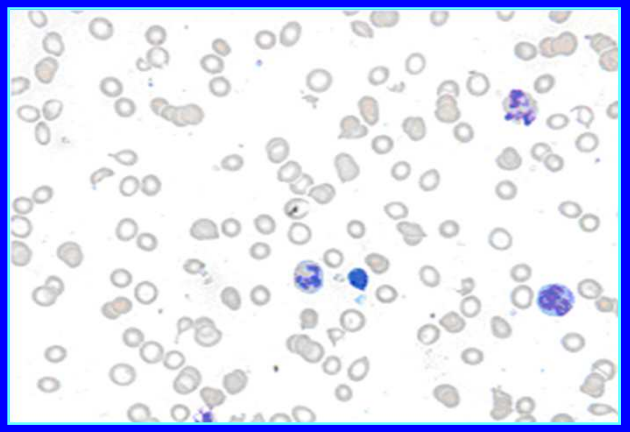
68 year old ♀ with CMML

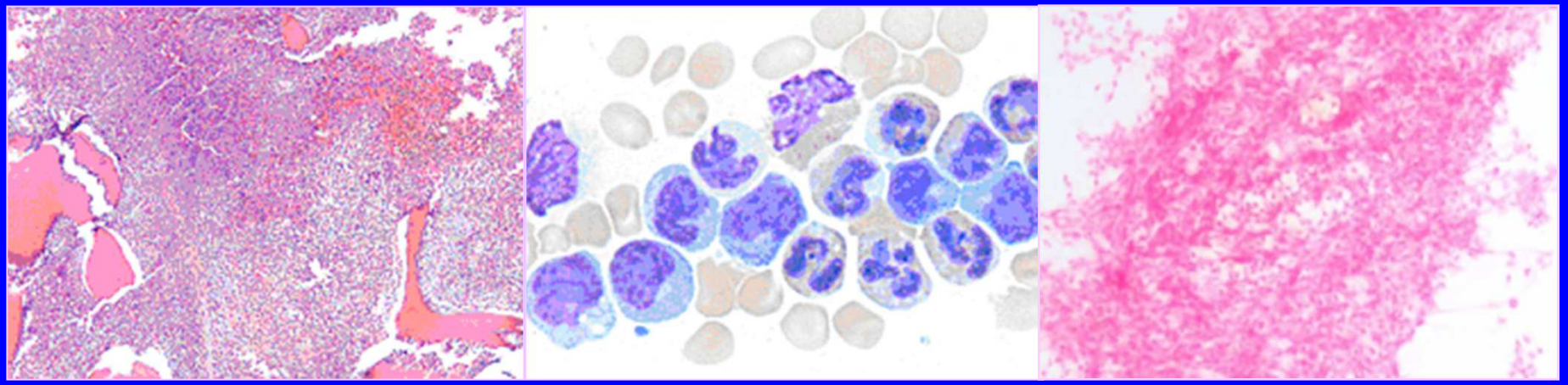
Peripheral Blood:

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



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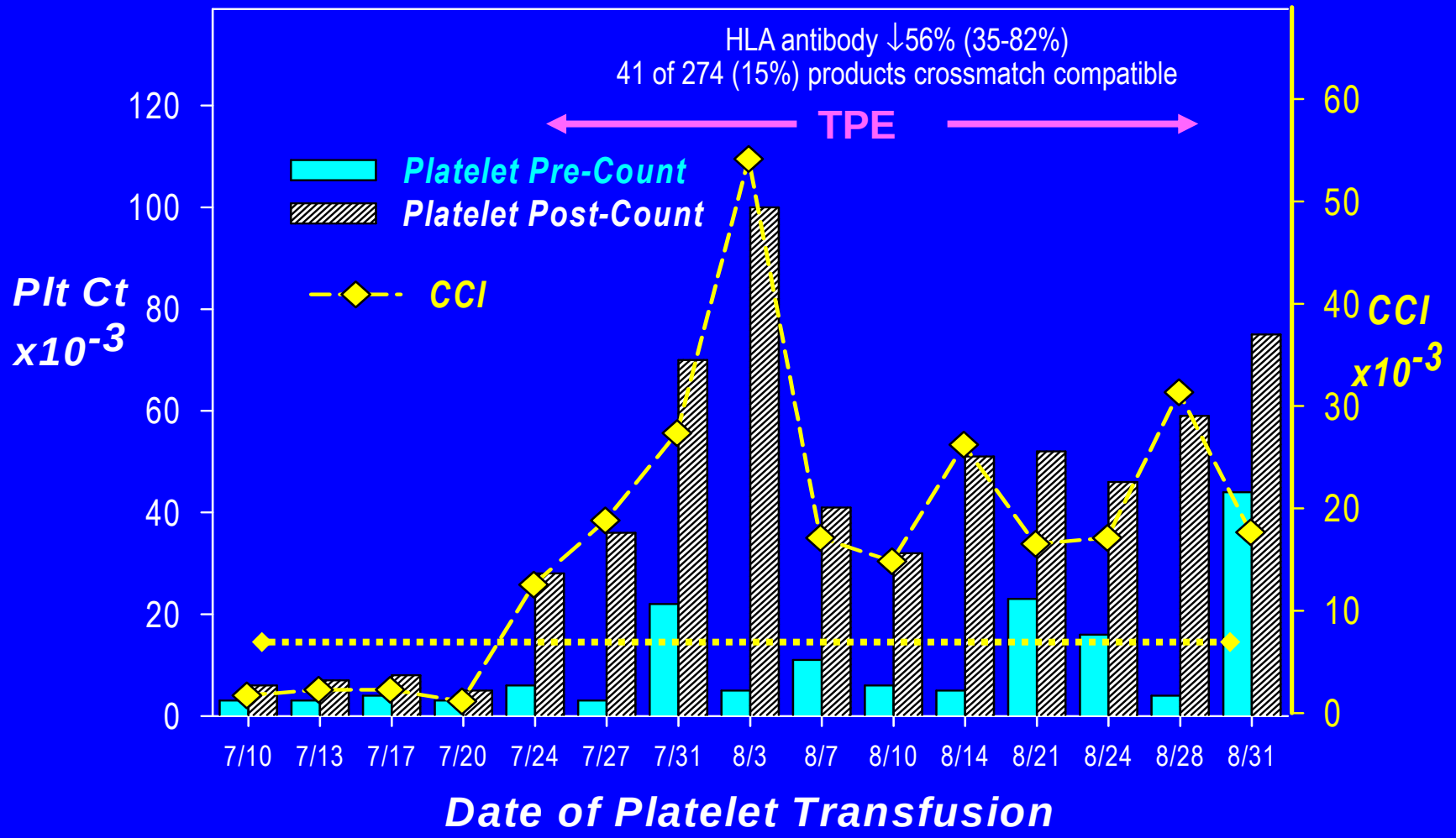
Platelet Support of Patient PK



Clinical Guidelines that are Useful…

- Assist clinicians in their decision making
- Provide guidance when Type I evidence is lacking
- Help to guide decision making for a patient who would have been excluded from existing Type I study
- Transparently take all of the evidence into account

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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

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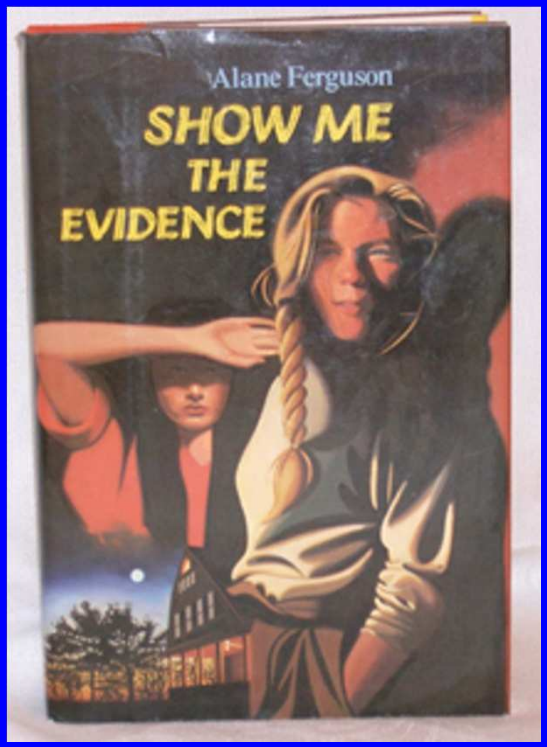
Apheresis at the Bedside

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



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