Therapeutic Plasma Exchange in Multiple Sclerosis Relapses

Mariusz Stasiołek

Neurology Department

Polish Mother's Memorial Hospital – Research Institute, Lodz

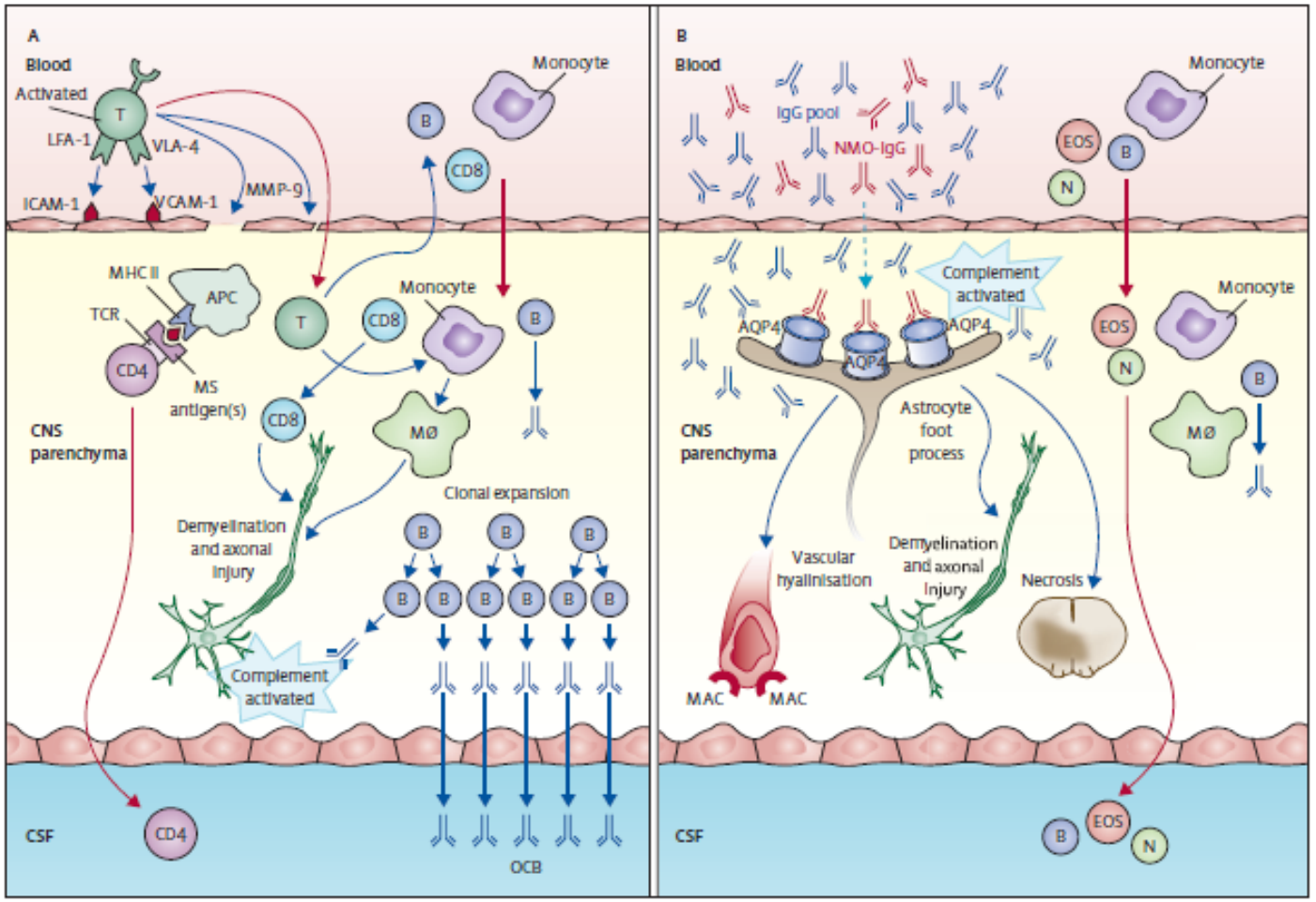
MS heterogeneity

- **Multiple Sclerosis – differences in clinical manifestation and pathological findings**
- **NMO spectrum disorders**

Unknown etiopathology:

- **autoaggression hypothesis?**
- **infection hypothesis?**
- **environmental factors?**
- **genetic predisposition?**

MS heterogeneity



Wingerchuk et al. Lancet Neurol. 2007:805-15.

Several patterns of CNS lesions in MS

Pattern I - macrophage and T lymphocyte infiltration

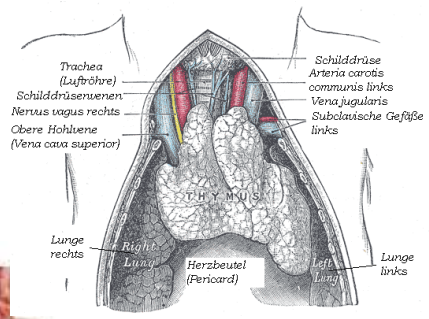
Pattern II - immunoglobulin deposition and complement activation

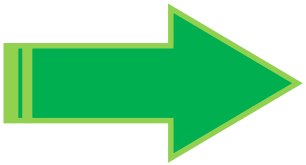
Pattern III - inflammatory, characterized by a selective loss of myelin-associated glycoprotein (MAG), reduction in oligodendrocyte density, oligodendrocyte apoptosis, and minimal remyelination

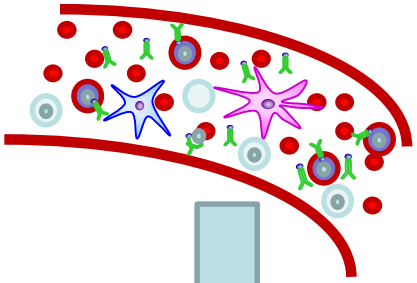
Pattern IV - nonapoptotic oligodendroglial death, possibly owing to metabolic or toxic factors

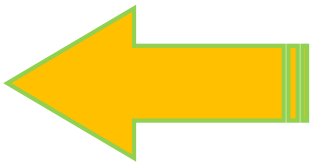
Lucchinetti et al. Ann Neurol 2000, 47:707–717.

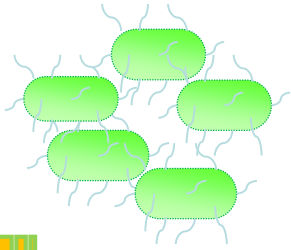
MS etiopathology

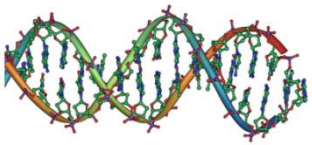


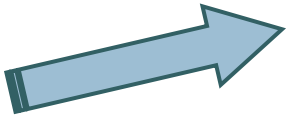


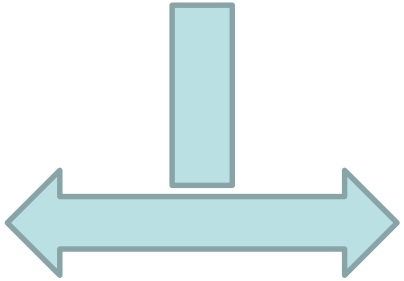












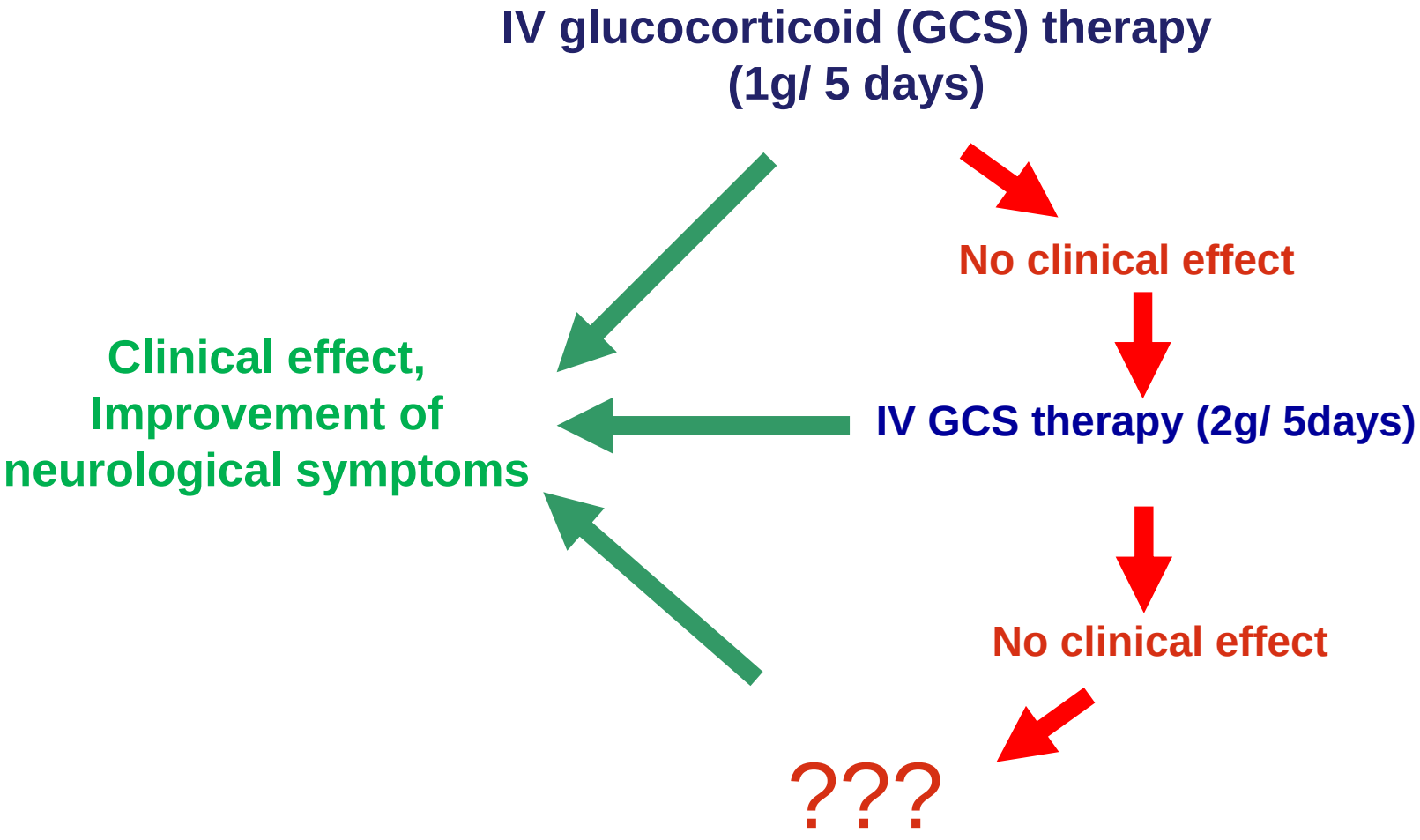
Immune reaction

Immune regulatory processes

Stabilisation

Relapse

MS – relapse treatment



Glucocorticoid (GCS) resistance

Hereditary GCS resistance

GCS-receptor (GR) mutations associated with impaired ligand binding, lower GR expression or lower DNA binding activity. High serum cortisol level without clinical features of hipercortisolim

Lamberts. Ann Endocrinol (Paris). 2001; 62:164-167.

Tissue and disease specific GCS resistance

Mainly inflammatory processes – no therapeutic effect but „normal" side effects

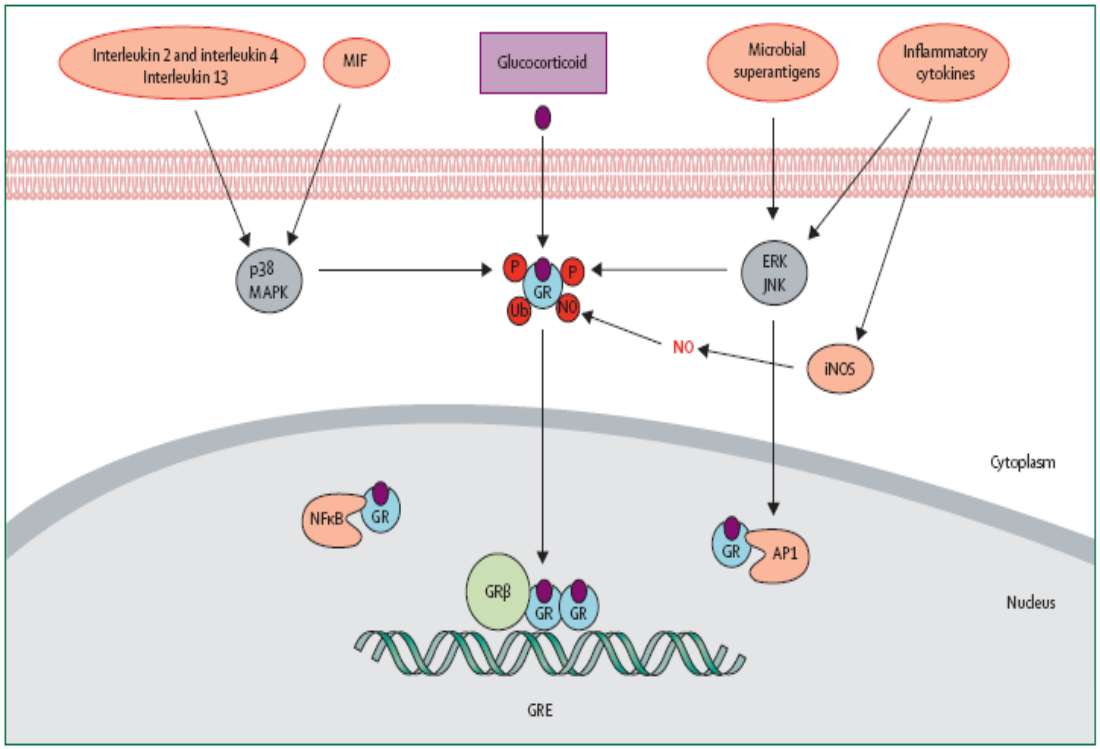
Barnes & Adcock. Lancet. 2009; 373:1905-1917.

GCS resistance in diseases typically well responding to GCS treatment

Chikanza IC. Ann N Y Acad Sci. 2002; 966:39-48.

GCS resistance

- **Disbalanced GR-isoforms structure (GRα, GRβ, GRγ)**
- **Structural changes of GR molecule associated with inflammatory factors**
- **GR interaction with other inflammatory molecules (e.g. transcriptional factors)**
- **Impairment of histon acetylation and deacetylation.**



Barnes & Adcock. Lancet. 2009; 373:1905-1917.

GCS resistance in MS

Dysregulation of the hypothalamo-pituitary-adrenal axis

- Elevated serum levels of cortisol and ACTH
- Impaired functional tests
- Without clinical features of hipercortisolism

Then Bergh et al. Neurology. 1999; 53:772-777.

Impaired influence of GCS on immune cells

- T cells apoptosis (progressive MS forms)
- Cytokine secretion (IL1, Il-6, TNFα, IFNγ)
- Unspecific proliferation responses

van Winsen LM et al. Mult Scler. 2010; 16:500-502.

Decreased affinity of GR – ligand binding

Ysrraelit MC et al. Neurology. 2008; 71:1948-1954.

Therapeutic plasma exchange (TPE)

Removal of multiple humoral factors from the systemic blood flow - including various immune active substances

Therapeutic plasma exchange (TPE)

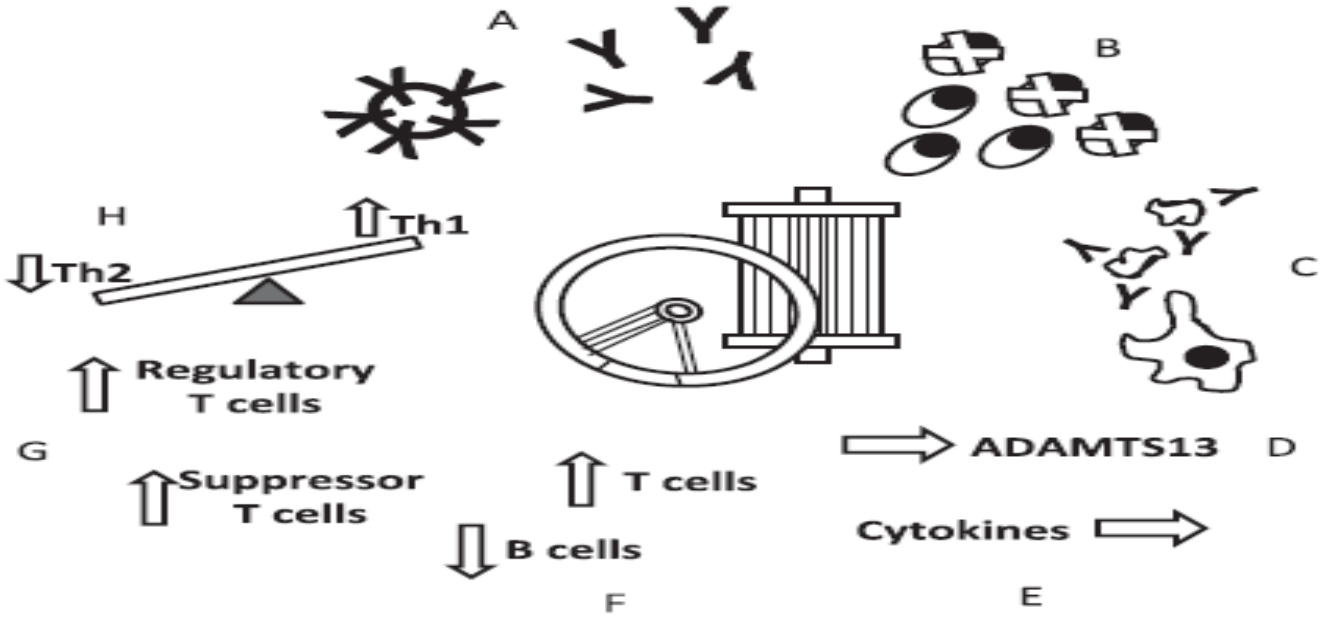


Fig 1. Possible mechanisms of plasma exchange. (A) Removal of pathological antibodies. (B) Stimulates the proliferation of B cells and plasma cells, sensitizing them to immunosuppressants. (C) Removal of immune complexes with enhanced macrophage/monocyte function. (D) Replacement of missing plasma components, such as ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motifs 13). (E) Removal of cytokines. (F) Changes in lymphocyte numbers. (G) Increased T regulatory cells and T suppressor activity. (H) Correction of altered T-helper cell type 1/2 (Th1/Th2) ratio favouring Th1 predominance.

Reeves and Winters, Br J Haematol 2014: 342-351.

TPE – acute CNS demyelination

Ann Neurol. 1999 Dec;46(6):878-86.

A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease.

Weinshenker BG, O'Brien PC, Petterson TM, Noseworthy JH, Lucchinetti CF, Dodick DW, Pineda AA, Stevens LN, Rodriguez M.

Randomized, sham-controlled, double-masked study of plasma exchange without concomitant immunosuppressive treatment in patients with recently acquired, severe neurological deficits resulting from **attacks of inflammatory demyelinating disease**, who failed to recover after treatment with intravenous corticosteroids.

Moderate or greater improvement in neurological disability in 8 of 19 **(42.1%)** cases of active treatment compared with 1 of 17 (5.9%) cases of sham treatment.

TPE – acute CNS demyelination

Efficacy proven in GCS refractory MS relapse as well as in optic neuritis and clinically isolated syndrome

Clinical improvement observed in up to over 70% patients with GCS refractory MS relapse

Beginning of symptoms' resolution typically already after 2nd-3rd TPE

Rodriguez et al. 1993; Weinshenker et al.1999; Keegan et al. 2002; Schilling et al. 2006; Ruprecht et al. 2004; Trebst et al. 2009; Roesner et al. 2011

Therapeutic effect shown also in patients with GCS-refractory superimposed relapses in secondary progressive multiple sclerosis

Linker et al. J Neurol 2007, 284:1288-9

Neurology. 2002 Jan 8;58(1):143-6.

Plasma exchange for severe attacks of CNS demyelination: predictors of response.

Keegan M, Pineda AA, McClelland RL, Darby CH, Rodriguez M, Weinshenker BG.

59 patients (Mayo Clinic 1984 2000) treated with TPE for acute, severe attacks of CNS demyelination

RR-MS (n = 22, 37.3%), NMO (n = 10, 16.9%), and acute disseminated encephalomyelitis (n = 10, 16.9%)

TPE was followed by moderate or marked functional improvement in 44.1% of treated patients

Improvement was positively associated with:

- Male sex (p = 0.021)
- preserved reflexes (p = 0.019)
- **early initiation of treatment (p = 0.009)**

Arch Neurol. 2011 Jul;68(7):870-8.

Beneficial plasma exchange response in central nervous system inflammatory demyelination.

Magaña SM, Keegan BM, Weinshenker BG, Erickson BJ, Pittock SJ, Lennon VA, Rodriguez M, Thomsen K, Weigand S, Mandrekar J, Linbo L, Lucchinetti CF.

Table 1. Clinical Spectrum of Plasma Exchange Cohort at Time of Plasma Exchange

Clinical Feature	All Subjects (N=153)	PLEX Responders (n=90)	PLEX Nonresponders (n=63)	PLEX Response Rate, %
Disease duration at PLEX, median (range)[a]	1.4 y (18 d to 38.5 y)	1.1 y (18 d to 32.9 y)	2.3 y (29 d to 38.5 y)	
Clinical course prior to PLEX, No. (%)				
Monophasic	43 (28)	27 (30)	16 (25)	63
Relapsing	104 (68)	60 (67)	44 (70)	58
Progressive[b]	5 (3)	2 (2)	3 (5)	40
Diagnosis at PLEX, No. (%)				
Definite MS	55 (36)	34 (38)	21 (33)	62
Probable MS	18 (12)	10 (11)	8 (13)	56
NMO	26 (17)	11 (12)	15 (24)	42
LETM	36 (24)	25 (28)	11 (17)	69
Recurrent ON	1 (1)	0	1 (2)	0
TM	9 (6)	6 (7)	3 (5)	67
ADEM	3 (2)	0	3 (5)	0
CIS	5 (3)	4 (4)	1 (2)	80
EDSS score at index attack, median (IQR)	8 (6.5-8.5)	8 (6.5-8.5)	8 (6-8.5)	

Abbreviations: ADEM, acute disseminated encephalomyelitis; CIS, clinically isolated syndrome; EDSS, Expanded Disability Status Scale; IQR, interquartile range; LETM, longitudinally extensive transverse myelitis; MS, multiple sclerosis; NMO, neuromyelitis optica; ON, optic neuritis; PLEX, plasma exchange; TM, transverse myelitis.

[a] $P \leq .05$.

[b] Four patients had a progressive course with superimposed attacks; 1 patient had a progressive course without superimposed attacks.

Results: 153 patients treated with TPE for a steroid-refractory CNS-IDD, of whom 90 (59%) exhibited moderate to marked functional neurological improvement within 6 months following treatment.

TPE – CNS demyelination

Overview of literature regarding plasma exchange.

Authors	n	Design	MS-Type	No. of treatments	Treated plasma volume (ml)	Outcome
Khatri et al., 1985	54	Double-blind controlled	Progressive	20	n.a.	EDSS-improvement
Weinshenker et al., 1999	36	Double-blind	Mixed	7	3000	Therapy response in 42% of patients
Weiner et al., 1989	116	Double-blind, multi-center, randomized	RRMS	11	n.a.	Significant improvement after 4 weeks
Ruprecht et al., 2004	10	Retrospective	Opticus neuritis	n.a.	n.a.	Response in 7 of 10 patients
Schilling et al., 2005	16	Retrospective	RRMS	5	3000	71% response rate
Trebst et al., 2009	20	Retrospective	RRMS	3–7	1.5-fold plasma volume	Response rate visual acuity 76%, other symptoms 87.5%
Habek et al., 2010	4	Retrospective	RRMS	5	2750	Improvement in 3 of 4 patients
Magaña et al., 2011	153	Retrospective	Mixed	7	n.a.	Response rate in 59%

Overview of published data on apheresis in children.

Authors	n	Diagnosis	Procedure	Steroid-refractory	Outcome
Takahashi et al., 1997	1	MS	PE	No	Free of Relapse for 18 months
Balestri et al., 2000	1	ADEM	PE	Yes	Neurological improvement
Miyazawa et al., 2001	1	ADEM	PE	Yes	Improvement of clinical and MRI features
Khurana et al., 2005	6	ADEM	PE	Yes	Substantial recovery in 5 of 6 children, 1 without deficits
Ramachandrannair et al., 2005	2	ADEM	PE	Yes	Complete clinical and radiological recovery
Mogami et al., 2011	1	MS	PE	Yes	Remarkable Improvement after 2nd of 7 PE
Koziolek et al., 2013	10	MS, ADEM, NMO	PE, IA	Yes	Significant improvement of EDSS & visual acuity

Muhlhausen et al. Atherpsclerosis Supp 2015

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY.

Evidence-based guideline update: Plasmapheresis in neurologic disorders

Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology

Plasmapheresis as adjunctive therapy is **probably effective** for management of exacerbations **in relapsing forms of MS** (…). plasmapheresis is **possibly effective** for **acute fulminant CNS demyelinating diseases (including MS, ADEM, NMO, and TM)** that fail to respond to high-dose corticosteroid treatment. (…) For chronic progressive or secondary progressive MS, plasmapheresis is established as ineffective based on consistent Class I evidence.

Recommendations.

- Plasmapheresis should be considered for the adjunctive treatment of exacerbations in **relapsing forms of MS (Level B).**
- Plasmapheresis may be considered in the treatment of **fulminant CNS demyelinating diseases** that fail to respond to high-dose corticosteroid treatment (Level C).
- Plasmapheresis should not be offered for **chronic progressive or secondary progressive MS (Level A).**

Journal of Clinical Apheresis 28:145–284 (2013)

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

Joseph Schwartz,[1] Jeffrey L. Winters,[2] Anand Padmanabhan,[3] Rasheed A. Balogun,[4] Meghan Delaney,[5] Michael L. Linenberger,[6] Zbigniew M. Szczepiorkowski,[7] Mark E. Williams,[8] Yanyun Wu,[9] and Beth H. Shaz[10,11]*

MULTIPLE SCLEROSIS

Incidence: 5–30/100,000/yr (US)	Condition	Procedure	Recommendation	Category
	Acute CNS inflammatory demyelinating disease unresponsive to steroids	TPE	Grade 1B	II
		IA	Grade 2C	III
	Chronic progressive	TPE	Grade 2B	III

# of reported patients*: >300	RCT	CT	CS	CR
Acute CNS inflammatory demyelinating disease	3 (306)	1 (41)	7 (86)	5 (5)
Chronic progressive	7 (285)	0	10 (165)	3 (4)

NEUROMYELITIS OPTICA

Incidence: Rare	Condition	Procedure	Recommendation	Category
	Acute	TPE	Grade 1B	II
	Maintenance	TPE	Grade 2C	III

# of reported patients*: 100–300	RCT	CT	CS	CR
Acute	0	2 (59)	11 (99)	29 (39)
Maintenance	0	0	1 (7)	1 (2)

TABLE I. Indications for Therapeutic Apheresis–ASFA 2013 Categories [1]

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.** *Example: plasma exchange in Guillain-Barre syndrome as 1st-line standalone therapy; plasma exchange in myasthenia gravis as 1st-line in conjunction with immunosuppression and cholinesterase inhibition*
II	**Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.** *Example: plasma exchange as standalone secondary treatment for acute disseminated encephalomyelitis after high-dose IV corticosteroid failure; extracorporeal photopheresis added to corticosteroids for unresponsive chronic graft-versus-host disease*
III	**Optimum role of apheresis therapy is not established. Decision making should be individualized.** *Example:extracorporeal photopheresis for nephrogenic systemic fibrosis; plasma exchange in patients with sepsis and multi-organ failure*
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.** *Example: plasma exchange for active rheumatoid arthritis*

Recommendation	Description
Grade 1A	Strong recommendation, high-quality evidence
Grade 1B	Strong recommendation, moderate quality evidence
Grade 1C	Strong recommendation, low-quality or very low- quality evidence
Grade 2A	Weak recommendation, high quality evidence
Grade 2B	Weak recommendation, moderate-quality evidence
Grade 2C	Weak recommendation, low-quality or very low-quality evidence

J Clin Apher. 2012; 27: 183-192

Maintenance plasma exchange therapy for steroid-refractory neuromyelitis optica.

Khatri BO, Kramer J, Dukic M, Palencia M, Verre W.

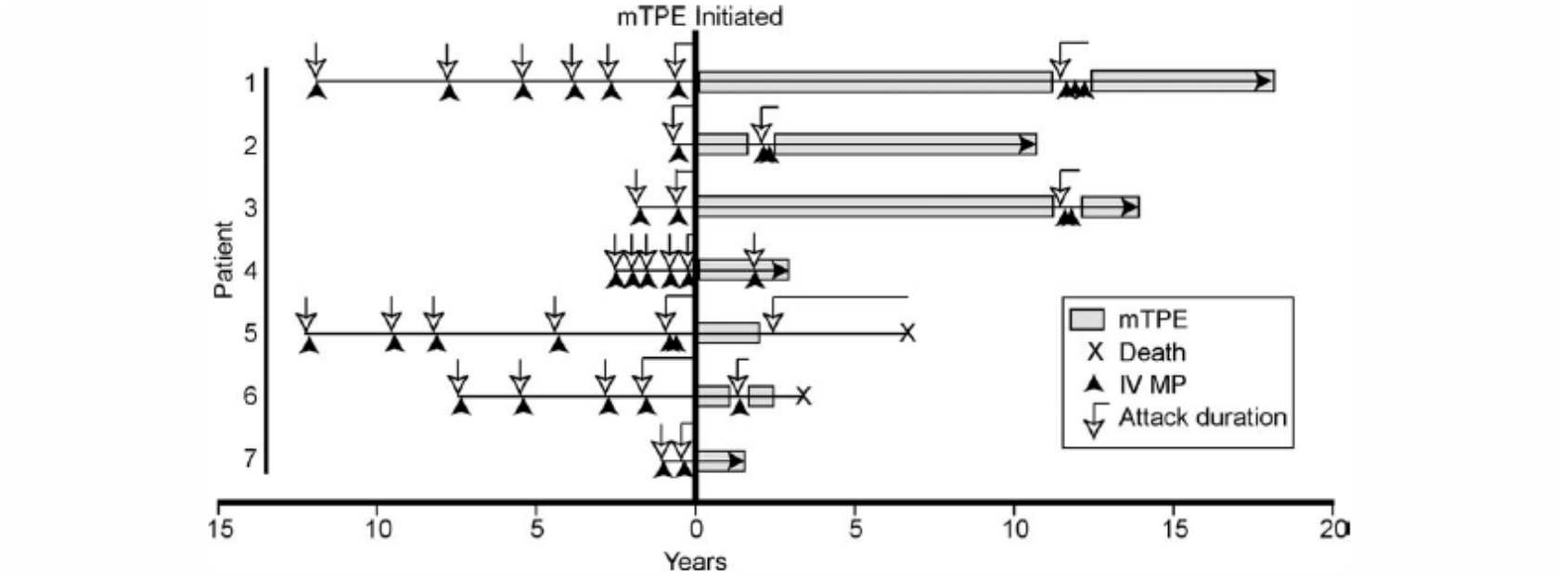


Fig. 1. Patients on the mTPE protocol experienced fewer exacerbations. Prior to enrollment in mTPE, all patients experienced a steroid-refractory attack of NMO. At initiation of mTPE, patients underwent induction protocol. Specifically, TPE three times a week for 2 weeks; two times a week for 2 weeks; then once a week for 3–5 weeks. After induction, TPE frequency was gradually tapered as dictated by the patient's clinical condition. Ultimately, patients on mTPE underwent exchange once every 3–12 weeks depending on the patient.

21 to 154 TPE over 2-16 years in 7 GCS-refractory NMO patients; 5/7 improved in EDSS; interruption resulted in clinical worsening

Multiple Sclerosis

Khatri et al., J Mult Scler 2014, 1:1
http://dx.doi.org/10.4172/jmso.1000102

Research Article Open Access

Plasma Exchange in Secondary Progressive Multiple Sclerosis: Twenty-Five Year Follow-Up Study

Bhupendra O Khatri[1*], Sergey Tarima[2], Michael P McQuillen[3], John Kramer[1], Mary Dukic[1] and Cynthia Bellanger[4]

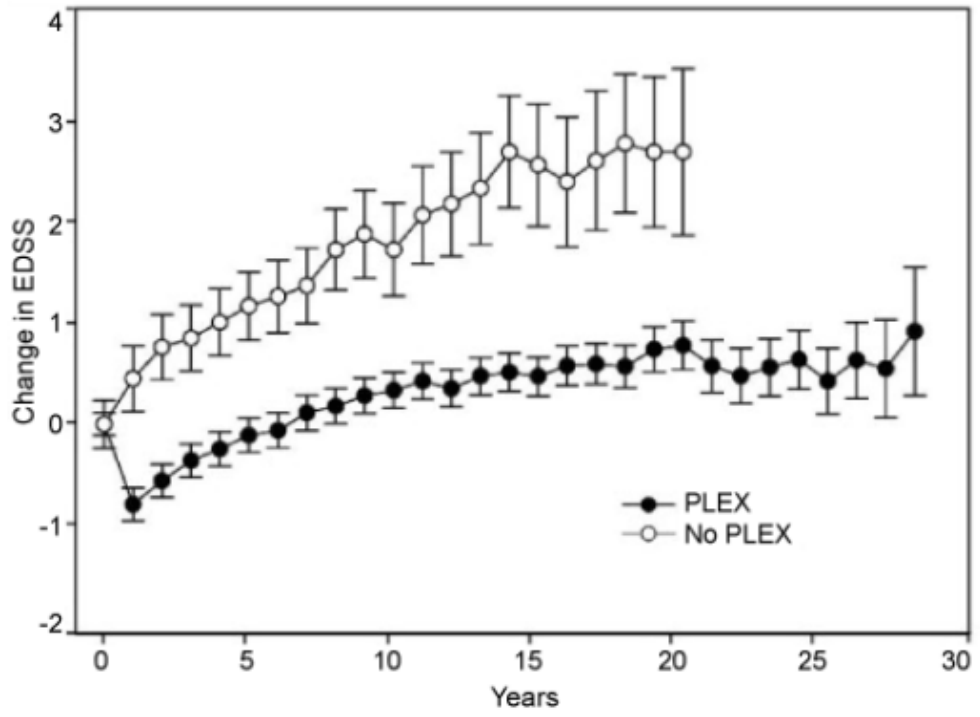
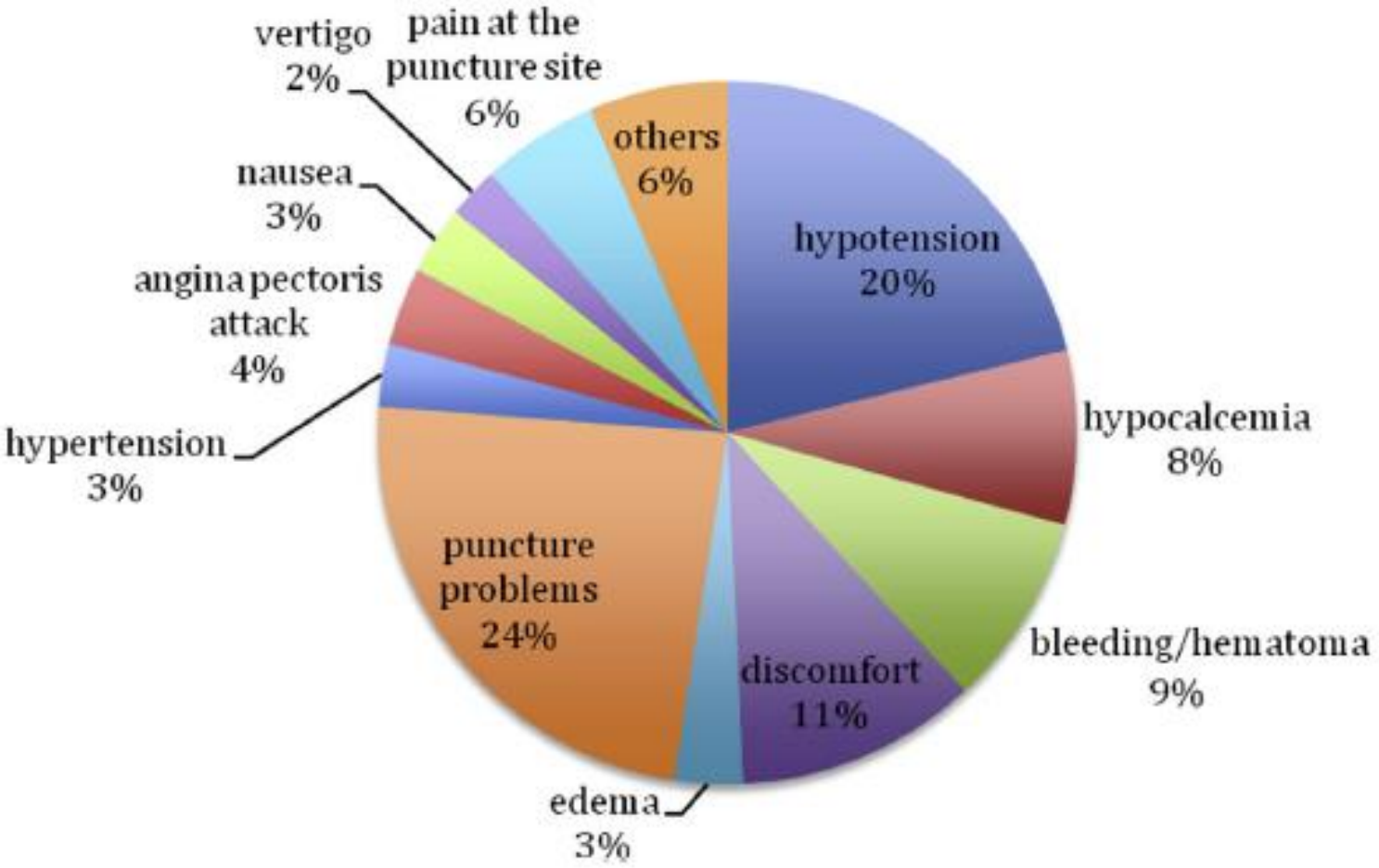


Figure 1: Over time, SPMS patients treated with PLEX incur less disability than control patients.

Retrospective unblinded analysis

- 271 + 42 patients
- TPE once weekly for 10 weeks
- Maintenance therapy
- 8709 TPE procedures
- No major adverse effects

Apheresis – adverse events



Diettrich-Riediger et al. Atherpsclerosis Supp 2015

MS – relapse treatment

Table 3. Plasma Exchange (PLEX) treatment

- Standard procedure
  The traditional PLEX treatment protocol for CNS inflammatory-demyelinating disease [22] consists of seven exchange treatments, every other day, for 14 days. In the interest of reducing hospital length of stay and cost, some centers will consider administering five to seven exchanges as frequently as every day with close monitoring for coagulopathy
- Complications
  Hypotension
  Anemia potentially requiring transfusion
  Thromboembolic events, including those related to heparin-induced thrombocytopenia
  Bleeding secondary to coagulopathy (fibrinogen levels are helpful to monitor in advance of reinfusion, especially with accelerated regimens; albumin replacement fluid does not contain fibrinogen)
  Infection, including line-related sepsis
  Central venous access-related complications
  It is advisable to hold ACE inhibitors for at least 24 h due to concern for flushing, GI symptoms, and hypotension, possibly related to the kinin pathway
  Infusion reactions/anaphylaxis, particularly if the replacement fluid involves donor plasma as opposed to albumin
  Hypocalcemia and arrhythmia (induced by citrate which is typically used as an anticoagulant in the filtration system or replacement fluid)
- Cost/cost effectiveness
  High cost due to procedural costs, equipment, replacement fluids, blood products, inpatient admission (at some centers), use of central access (at some centers)

Bevan and Gelfand.
Curr Treat Opt Neurol. 2015

Several patterns of CNS lesions in MS

Pattern I - macrophage and T lymphocyte infiltration

Pattern II - immunoglobulin deposition and complement activation

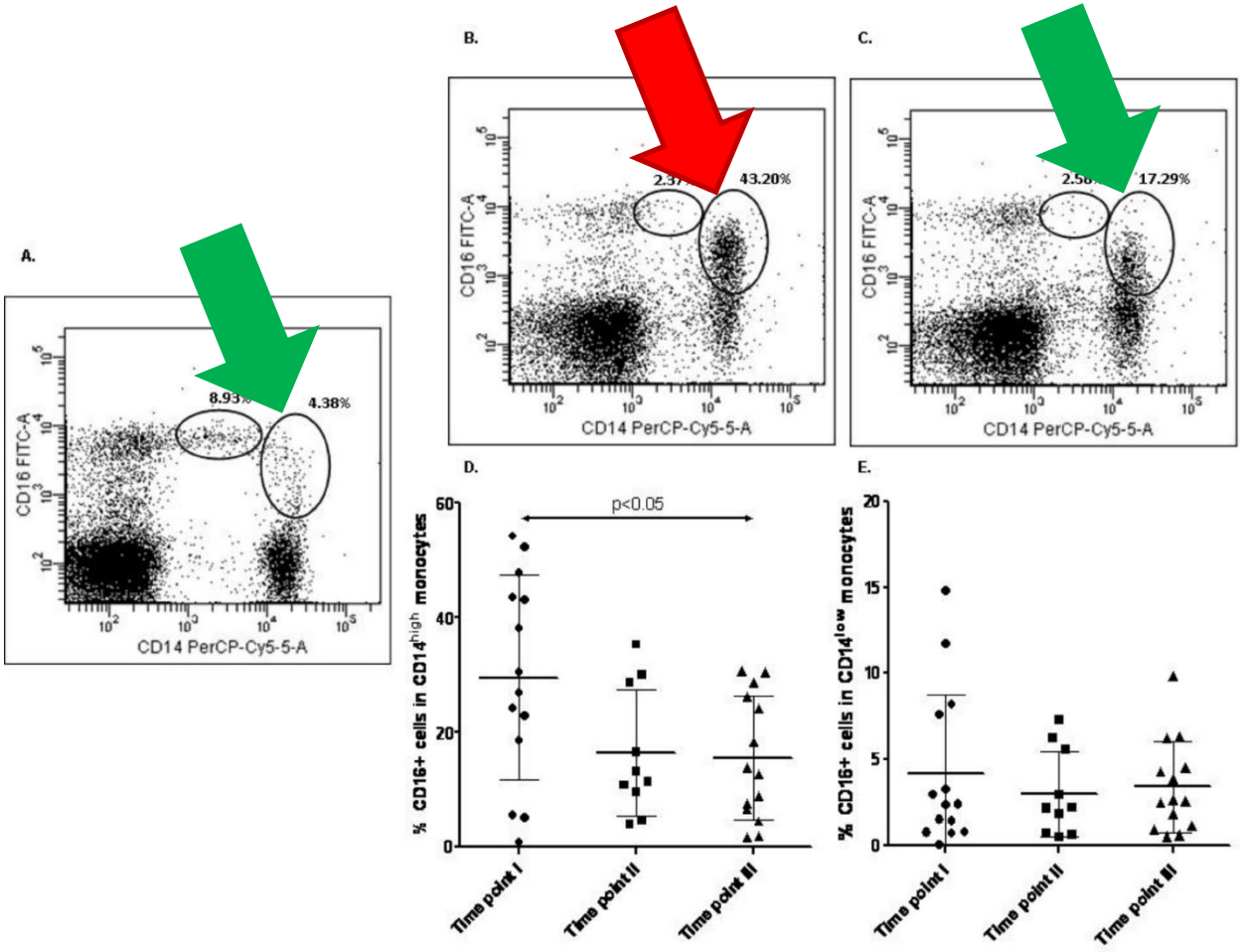
Pattern III - inflammatory, characterized by a selective loss of myelin-associated glycoprotein (MAG), reduction in oligodendrocyte density, oligodendrocyte apoptosis, and minimal remyelination

Pattern IV - nonapoptotic oligodendroglial death, possibly owing to metabolic or toxic factors

Keegan,…, Lucchinetti. Lancet 2005:579–582.

Lucchinetti et al. Ann Neurol 2000:707–717.

Therapeutic plasma exchange (TPE)



Stasiolek, Folia Med. Lodz. 2011

MS – relapse treatment

TIME
2 weeks?

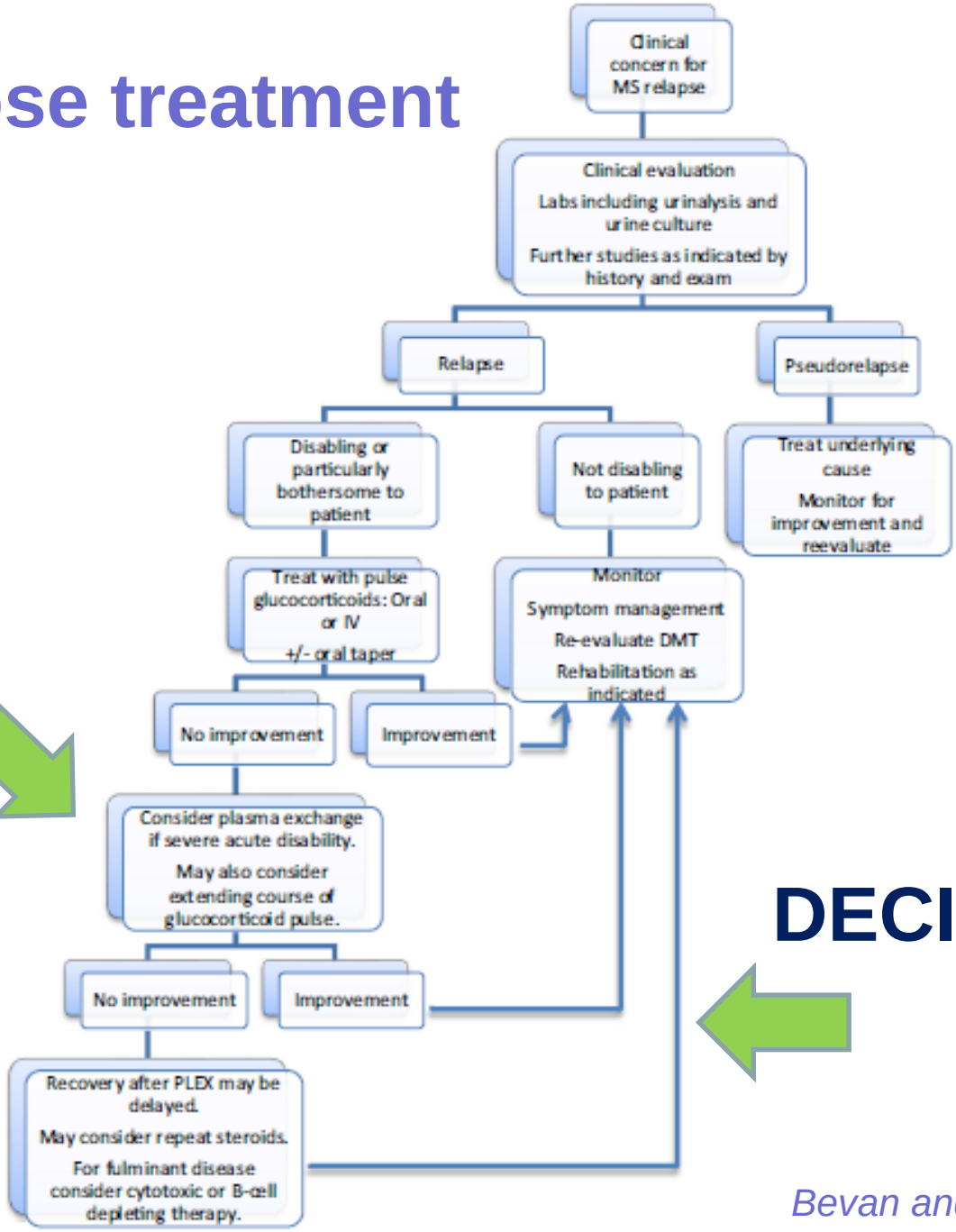


Fig. 1. An algorithmic approach to treating severe MS relapses.

DECISIONS!

Bevan and Gelfand.
Curr Treat Opt Neurol. 2015

ClinicalTrials.gov

Plasma Exchanges in Multiple Sclerosis (MS) Relapses (PLASMASEP)
NCT01442233

Maintenance Plasma Exchange for Neuromyelitis Optica (MultiPLEX)
NCT01500681


THANK YOU