Therapeutic Plasma Exchange in ICU

Bin Du, MD

Medical ICU

Peking Union Medical College Hospital

Conflicts of Interest

- None

History

- Apheresis (ἄφαιρεσις)
  - To take away
  - Method of obtaining one or more blood components by machine processing of whole blood in which the residual components of the blood are returned to the donor/patient during or at the end of the process

European Committee on Blood Transfusion. Guide to the preparation, use and quality assurance of blood components. 2010 16th Ed.

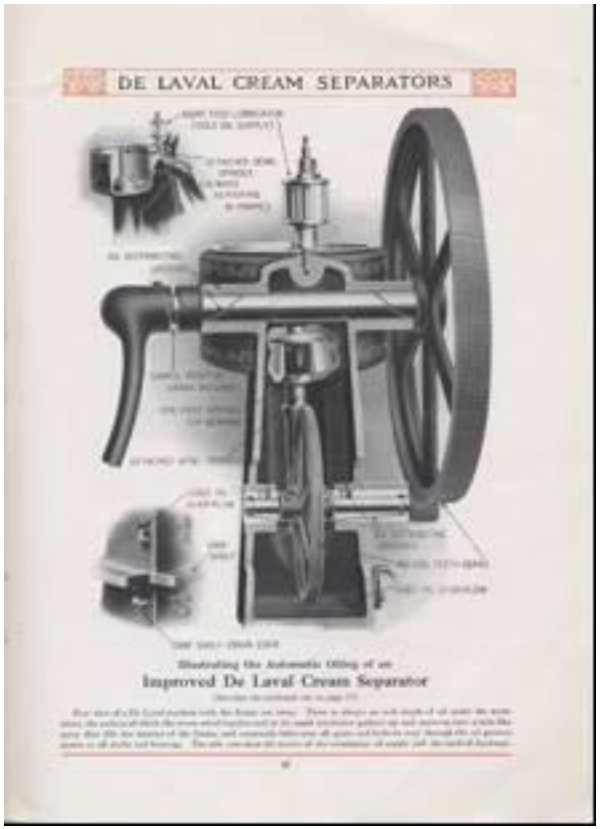
Apheresis in Ancient Medicine

- Disease reflects presence of disease-causing factors in the blood
- Selective blood letting (apheresis) should initiate cure

Figure 2-2 Athenian vase (fifth century B.C.). Depicts a physician about to bleed a patient. Below the patient is an ancient bleeding bowl. (Courtesy of Maurice Chuzeville, Paris, and reproduced with the permission of the Secretary General of the Louvre Museum, Paris.)

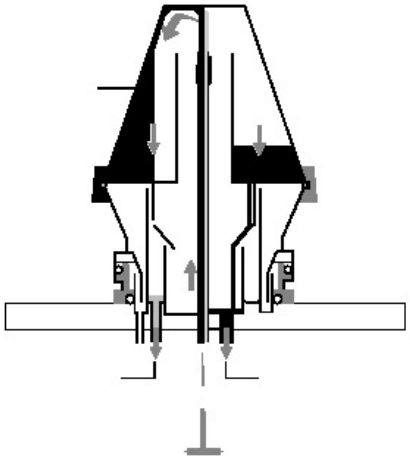
History

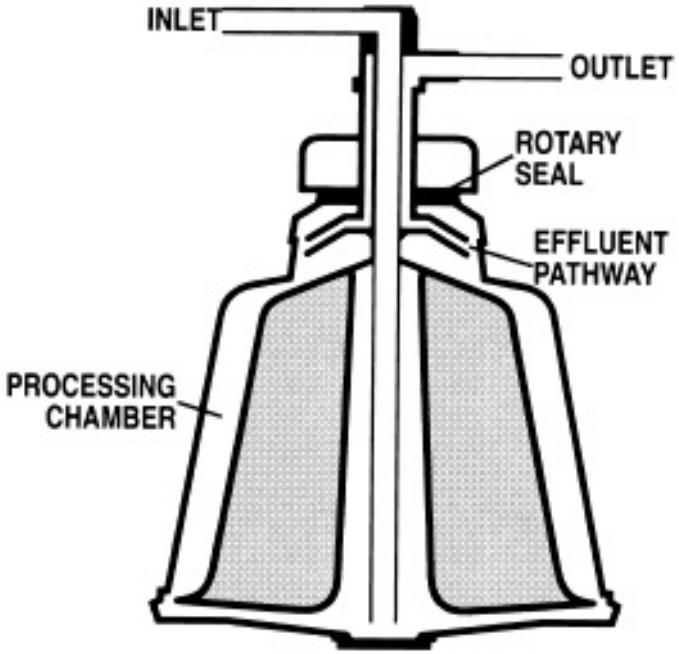
- 1877 de Laval



History

- 1877 de Laval
- 1950s Dr. Edwin Cohn
  Alan Latham

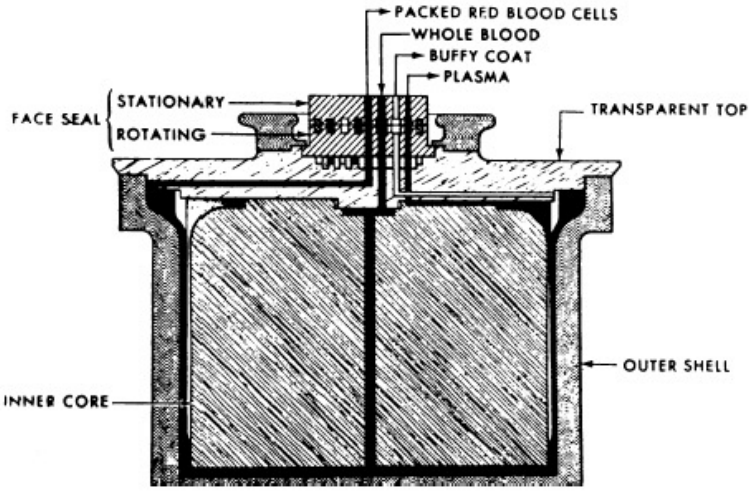




McLeod BC. Therapeutic apheresis: history, clinical application, and lingering uncertainties. Transfusion 2010; 50: 1413-1426

History

- 1877 de Laval
- 1950s Dr. Edwin Cohn
  Alan Latham
- 1960s Dr. Emil Freireich
  George Judson
  (an IBM engineer whose son being treated for CML)

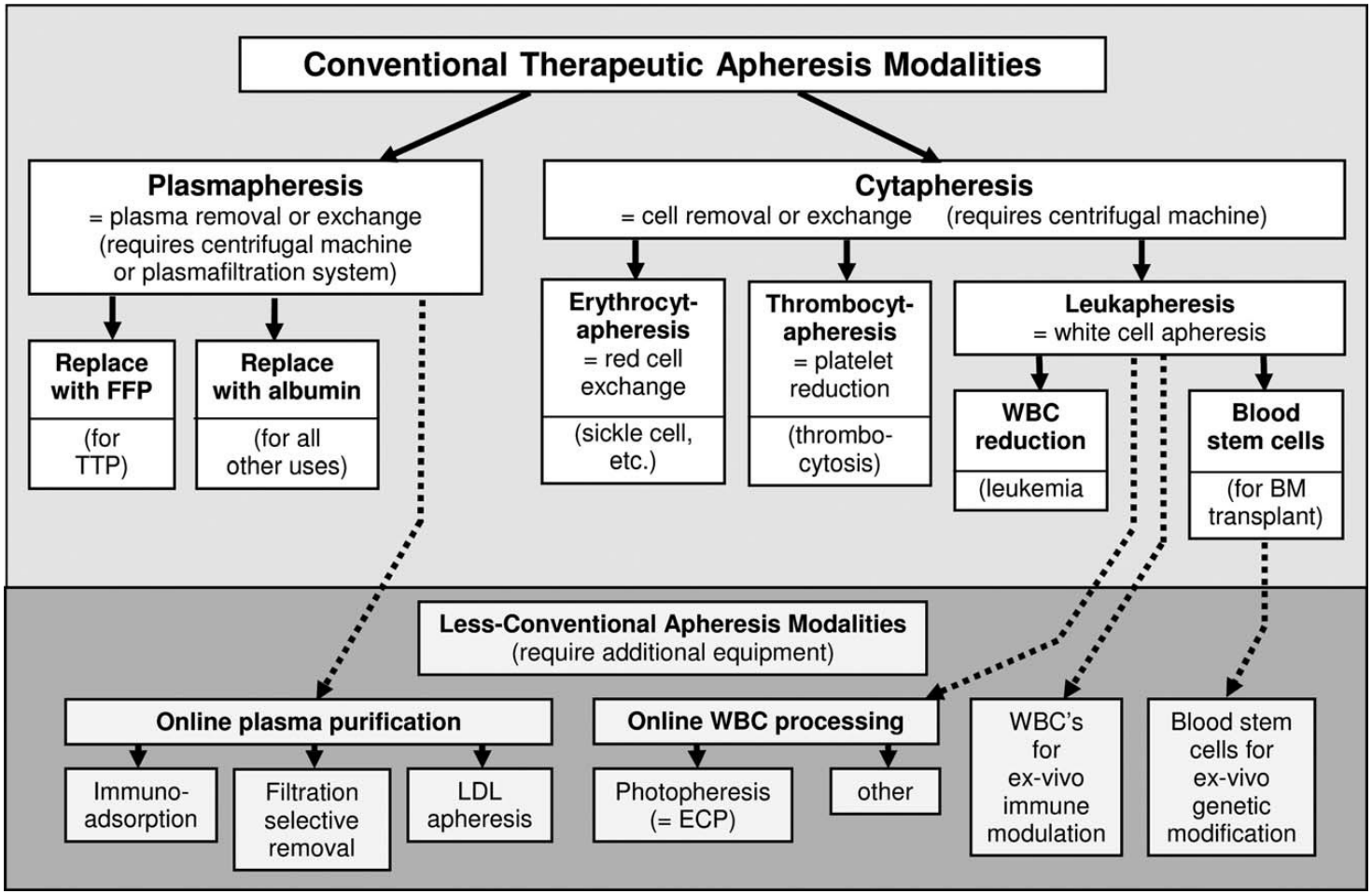


McLeod BC. Therapeutic apheresis: history, clinical application, and lingering uncertainties. Transfusion 2010; 50: 1413-1426

Terminology

- Apheresis: an umbrella term for ‘taking away’ a blood component. From Roman aphairesis meaning to take away by force
- Plasmapheresis: a general term used to denote the automated, selective removal of plasma. Plasmapheresis uses centrifugation to separate the blood components, in contrast to dialysis, which uses filtration to separate small molecules from the blood
- Plasma exchange (also called therapeutic plasma exchange [TPE]): removal of patient plasma and replacement with another fluid (e.g. donor plasma, colloid, crystalloid)

Conventional Therapeutic Apheresis



Okafor C, Ward DM, Mokrzycki MH, et al. Introduction and overview of therapeutic apheresis. J Clin Apheresis 2010; 25: 240-249

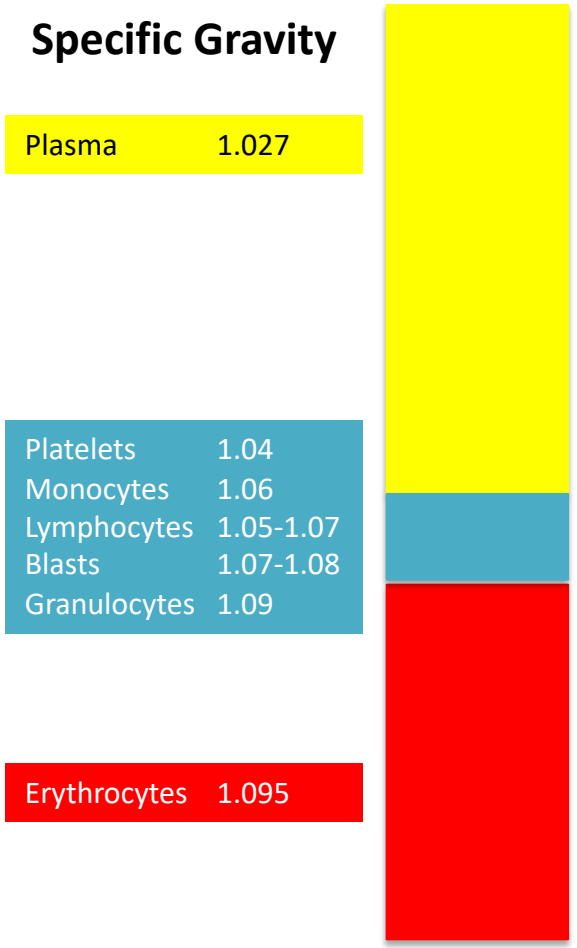
Mechanism of Action

Stoke's Law

$$Sv = \frac{2\,\omega^2\,R\,r^2(\rho_{cell} - \rho_{plasma})}{9\mu}$$

whereas
Sv: cellular velocity of sedimentation
$\omega^2 R$: centrifugal acceleration or g
r: cell radius
$\rho_{cell} - \rho_{plasma}$: difference between the density of cell and plasma
μ: inverse of the fluid viscosity

Centrifugal separation as a function of
- Sv
- Dwell time (inverse of inlet blood flow rate)



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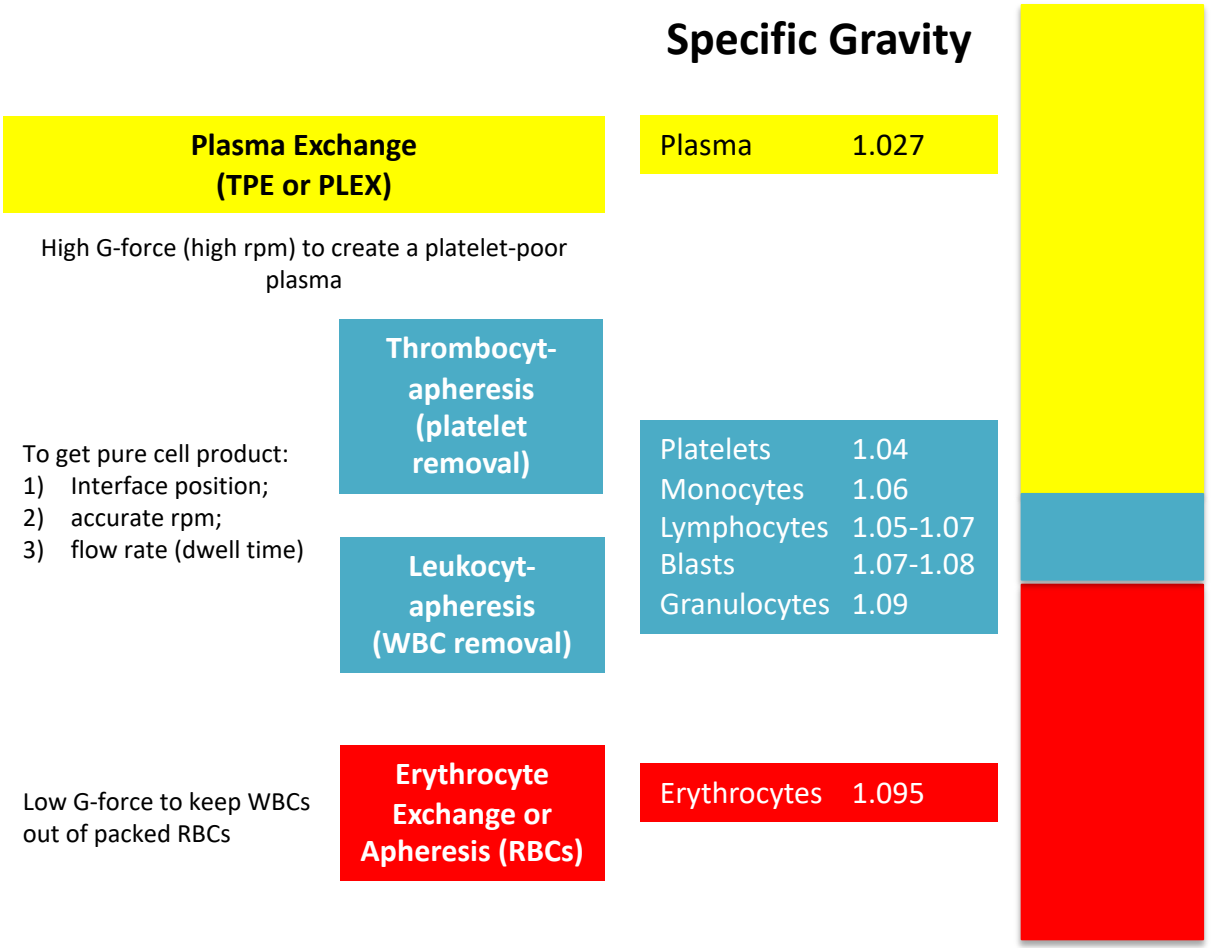
Mechanism of Action



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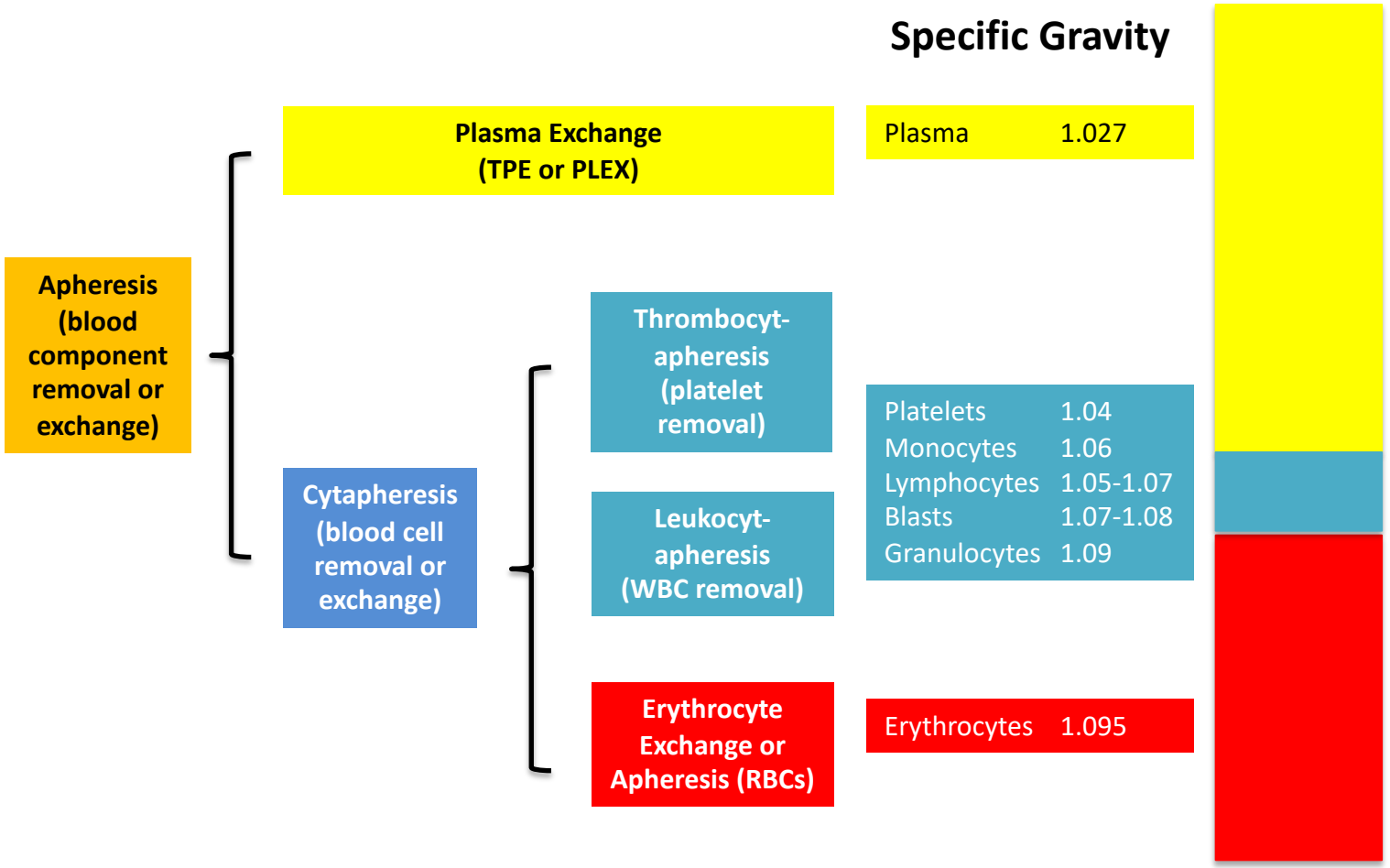
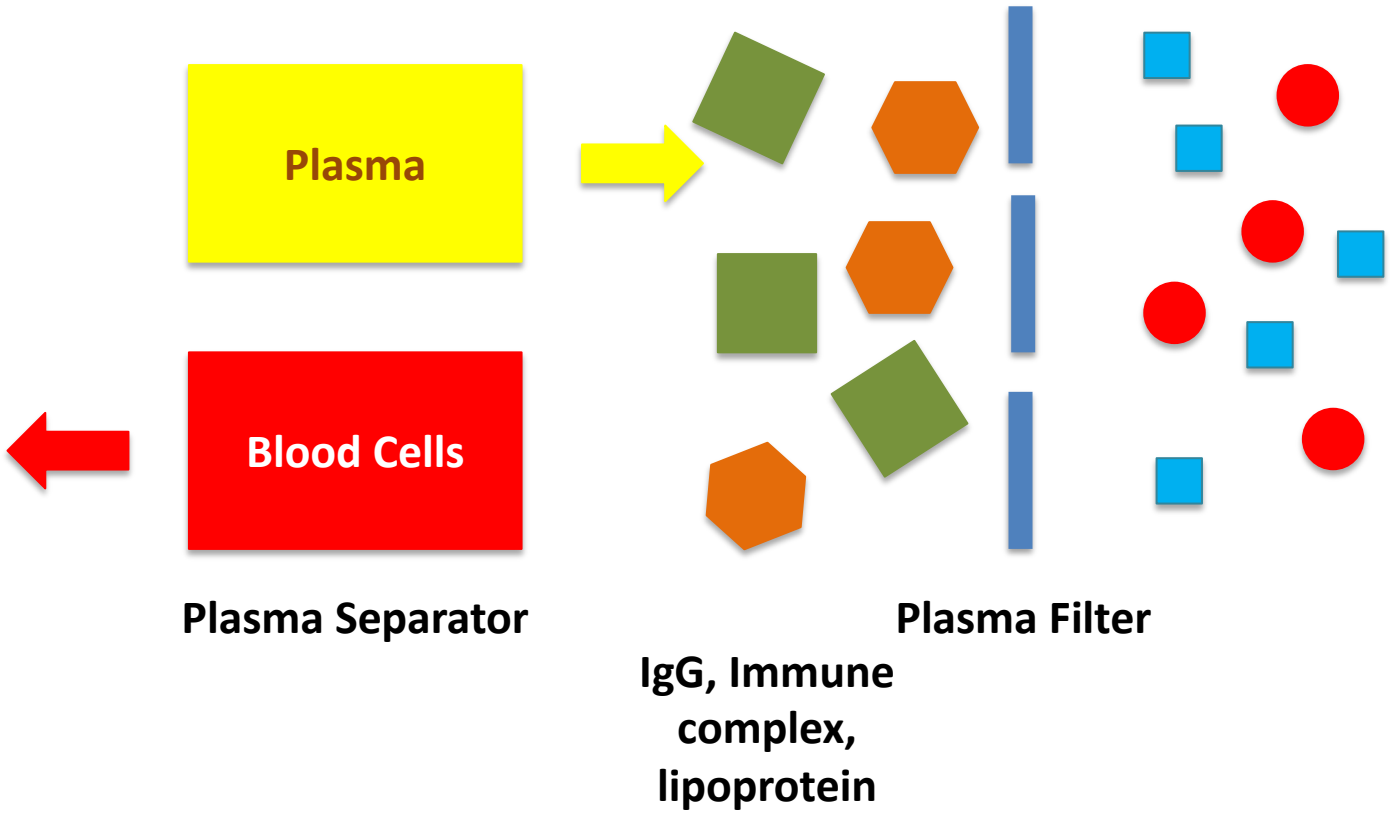
Mechanism of Action



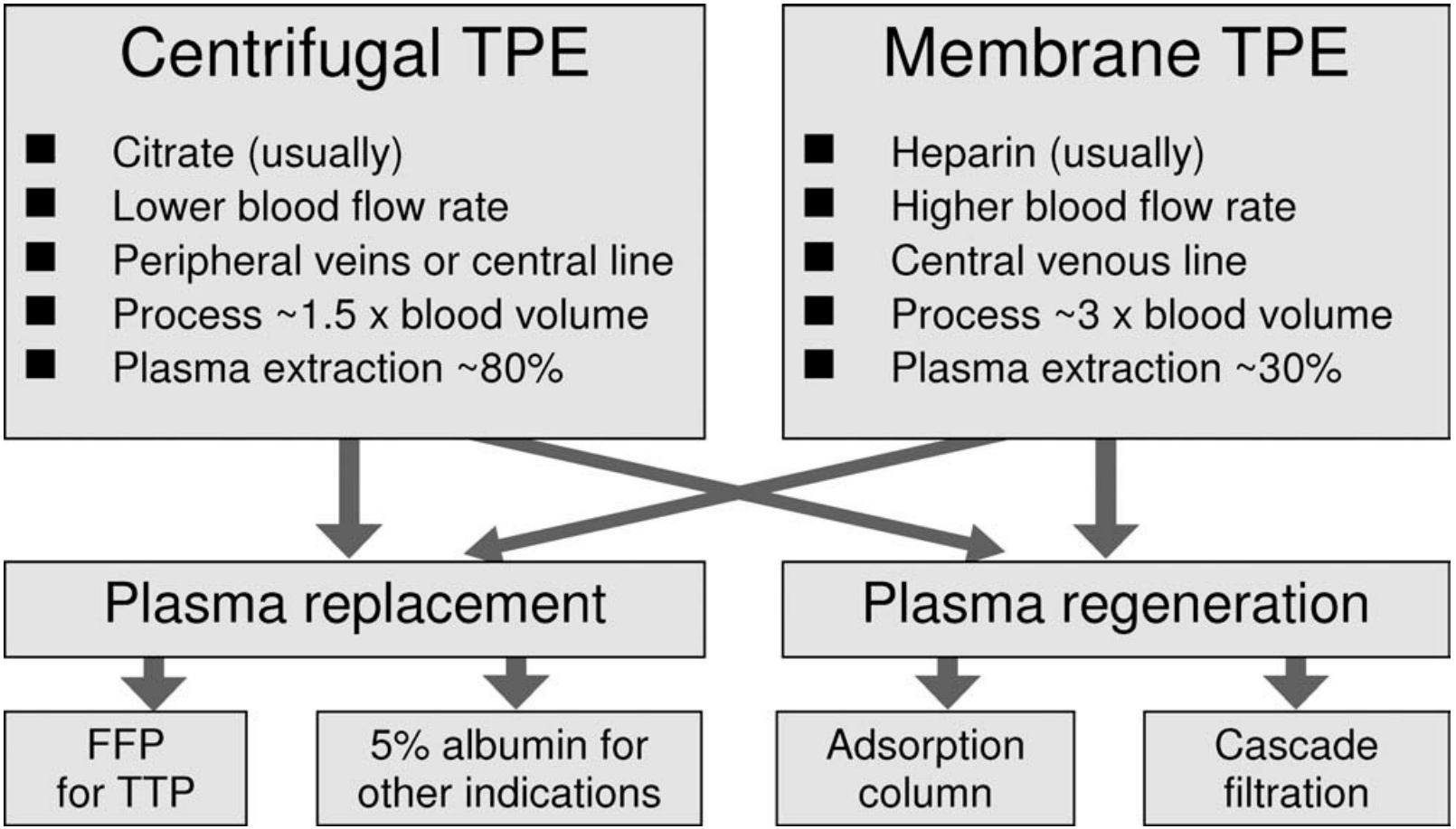
Okafor C, Ward DM, Mokrzycki MH, et al. Introduction and overview of therapeutic apheresis. J Clin Apheresis 2010; 25: 240-249

Mechanism of Action

Double Filtration Plasmapheresis



Centrifugal vs. Membrane PE



Ward DM. Conventional apheresis therapies: a review. J Clin Apheresis 2011; 26: 230-238

Choice of Replacement Solution

FFP (Fresh-Frozen Plasma)

- To replace deficient or defective plasma constituents: use FFP for whole replacement volume. Examples: TTP (thrombotic thrombocytopenic purpura), other thrombotic microangiopathies
- To prevent exacerbating active lung hemorrhage: use FFP for all or part of replacement volume. Examples: Goodpasture‘s syndrome, ANCA vasculitis

Albumin (or other colloid)

- Use for most applications
- Either 5% albumin for whole replacement volume
- Or one-quarter saline and three-quarters 5% albumin
- Or other colloidal solution
- If needed for clotting factor depletion, give 2 units FFP as last part of replacement volume (e.g. if fibrinogen at start is < 110 mg/dL)

Effectiveness of TPE

- Volume of plasma removed relative to total plasma volume
- Distribution of substance to be removed
  - Between intra and extravascular compartments
- Speed at which the substance equilibrates between compartments
- Rate at which then substance is synthesized

Dose of Therapeutic Plasma Exchange

Prescribed volume of each plasma exchange procedure **x** **Number and frequency of procedures** **= DOSE**

- Patient size (plasma volume)

- Pathogenic molecule
- Volume of distribution
- Disease characteristics

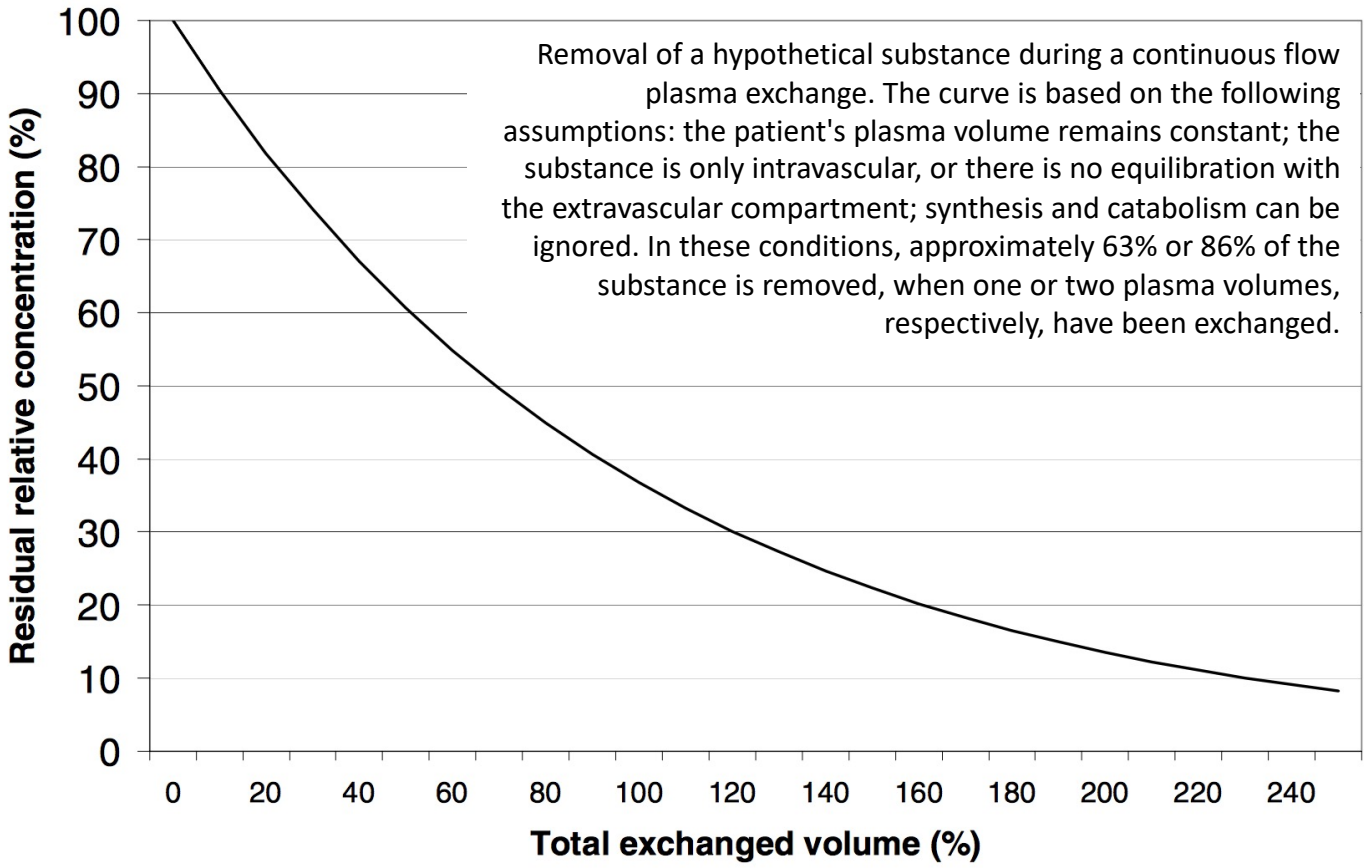
example

"volume to remove: 3.5 liters"

example

"Rx daily x 3, then qod x 3, then reassess"

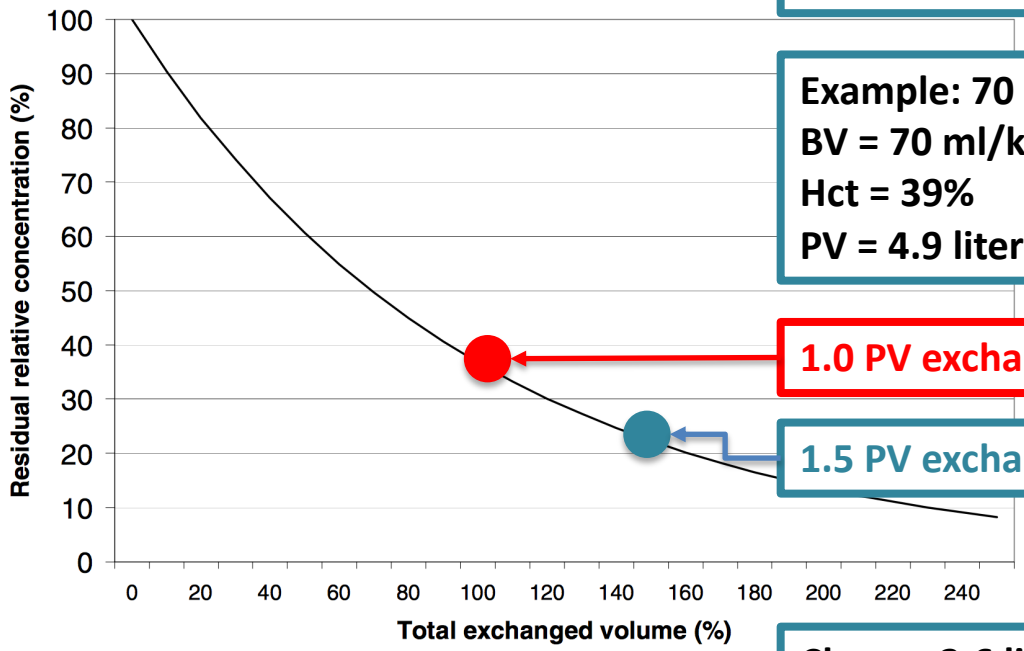
Removal Kinetics of TPE



Reverberi R, Reverberi L. Removal kinetics of therapeutic apheresis. Blood Transfus 2007; 5: 164-174

Prescription of Each TPE Procedure

Kinetics of Plasma Removal



- A 1.0-volume exchange removes 63%
- A 1.5-volume exchange removes 78%

Adult blood volume (BV) ~ 70 ml/kg
Plasma volume (PV) = BV x (1 – Hct)

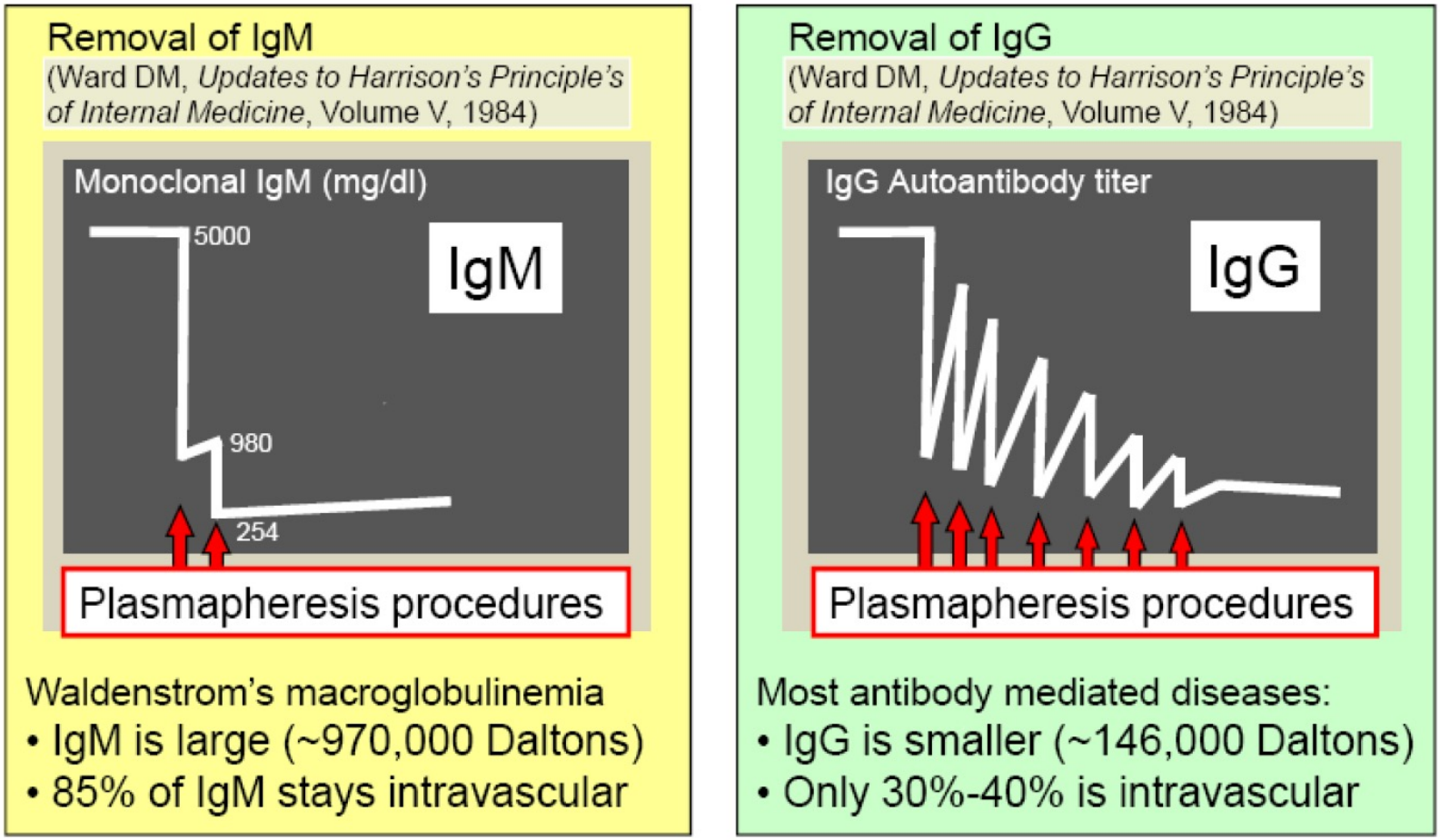
Example: 70 kg female
BV = 70 ml/kg x 70 kg = 4.9 Liter
Hct = 39%
PV = 4.9 liter x 61% = 3 liter

1.0 PV exchange = 3 liters

1.5 PV exchange = 4.5 liters

Choose 3.6 liter TPE
X = 3.6 x 3.0 = 1.2
$Y = e^{-x} = e^{-1.2} = 0.30$
Therefore removes 70%

Effect of TPE/PLEX on Immunoglobulins



Kaplan AA. Therapeutic plasma exchange: core curriculum 2008. Am J Kidney Dis 2008; 52: 1180-1196

Metabolism of Plasma Proteins

Protein	Concentration (mg/mL)	MW × 103 d	Intravascular (%)	Fractional Turnover Rate (%/d)	Half-life (d)
Normal physiology					
IgG (except IgG3 subclass)	12	150	45	7	22
IgG3	0.7	150	64	17	7
IgMa	0.9	950	78	19	5
IgA	2.5	160	42	25	6
IgD	0.02	175	75	37	2.8
IgE	0.0001	190	45	94	2.5
Albumin	45	66	44	11	17
C3	1.4	240	67	41	2
C4	0.5	200	66	43	2
Fibrinogen	3-4	340	81	24	4.2
Factor VIII	0.1	100-340	71	150	0.6
Antithrombin III	0.2	56-58	45	55	2.4
Lipoprotein cholesterol	1.5-2.0	1,300	>90		3-5
Pathological conditions					
Macroglobulinemia, IgM	50-130	950	89	25*	5.9
Bence-Jones protein	4-10	10-25	<50	†	†
Endotoxin	3-25 × 10-7	100-2,400*	>50	‡	‡
Immune complexes	*	>300*	>50	‡	‡
Tumor necrosis factor	3-5 × 10-7	50 (trimer)	<50		6-20 min

Kaplan AA. Therapeutic plasma exchange: core curriculum 2008. Am J Kidney Dis 2008; 52: 1180-1196

Category Definition for TPE

TABLE II. 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.

Schwartz J, Padmanabhan A, Aqui N, et al. Guidelines on the use of therapeutic apheresis in clinical practice – evidence-based approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue. J Clin Apheresis 2016; 31: 149-338

GRADE Recommendation

TABLE III. Grading Recommendations Adopted from Guyatt et al. [4,9]

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

Schwartz J, Padmanabhan A, Aqui N, et al. Guidelines on the use of therapeutic apheresis in clinical practice – evidence-based approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue. J Clin Apheresis 2016; 31: 149-338

Indications of Therapeutic Plasma Exchange

CATEGORY I

Disorders for which apheresis is accepted as first-line therapy, either as a primary stand alone treatment or in conjunction with other modes of treatment

- Guillain-Barré syndrome
- Myasthenia gravis
- Chronic inflammatory demyelinating polyneuropathy
- Hyperviscosity in monoclonal gammopathies
- Thrombotic thrombocytopenic purpura
- Goodpasture syndrome (unless it is dialysis-dependent and there is no diffuse alveolar hemorrhage)
- Hemolytic uremic syndrome (atypical, due to autoantibody to factor H)
- Wilson disease, fulminant

Indications of Therapeutic Plasma Exchange

CATEGORY II

Disorders for which apheresis is accepted as second-line therapy, either as a stand alone treatment or in conjunction with other modes of treatment

- Lambert-Eaton myasthenic syndrome
- Multiple sclerosis (acute central nervous system demyelination disease unresponsive to steroids)
- RBC alloimmunization in pregnancy
- Mushroom poisoning
- Acute disseminated encephalomyelitis
- Hemolytic uremic syndrome (atypical, due to complement factor mutations)
- Autoimmune hemolytic anemia (life-threatening cold agglutinin disease)
- Systemic lupus erythematosus (severe)
- Myeloma cast nephropathy

Indications of Therapeutic Plasma Exchange

CATEGORY III

Optimum role of apheresis therapy is not established; decision-making should be individualized

- Posttransfusion purpura
- Autoimmune hemolytic anemia (warm autoimmune hemolytic anemia)
- Hypertriglyceridemic pancreatitis
- Thyroid storm

Indications of Therapeutic Plasma Exchange

CATEGORY IV

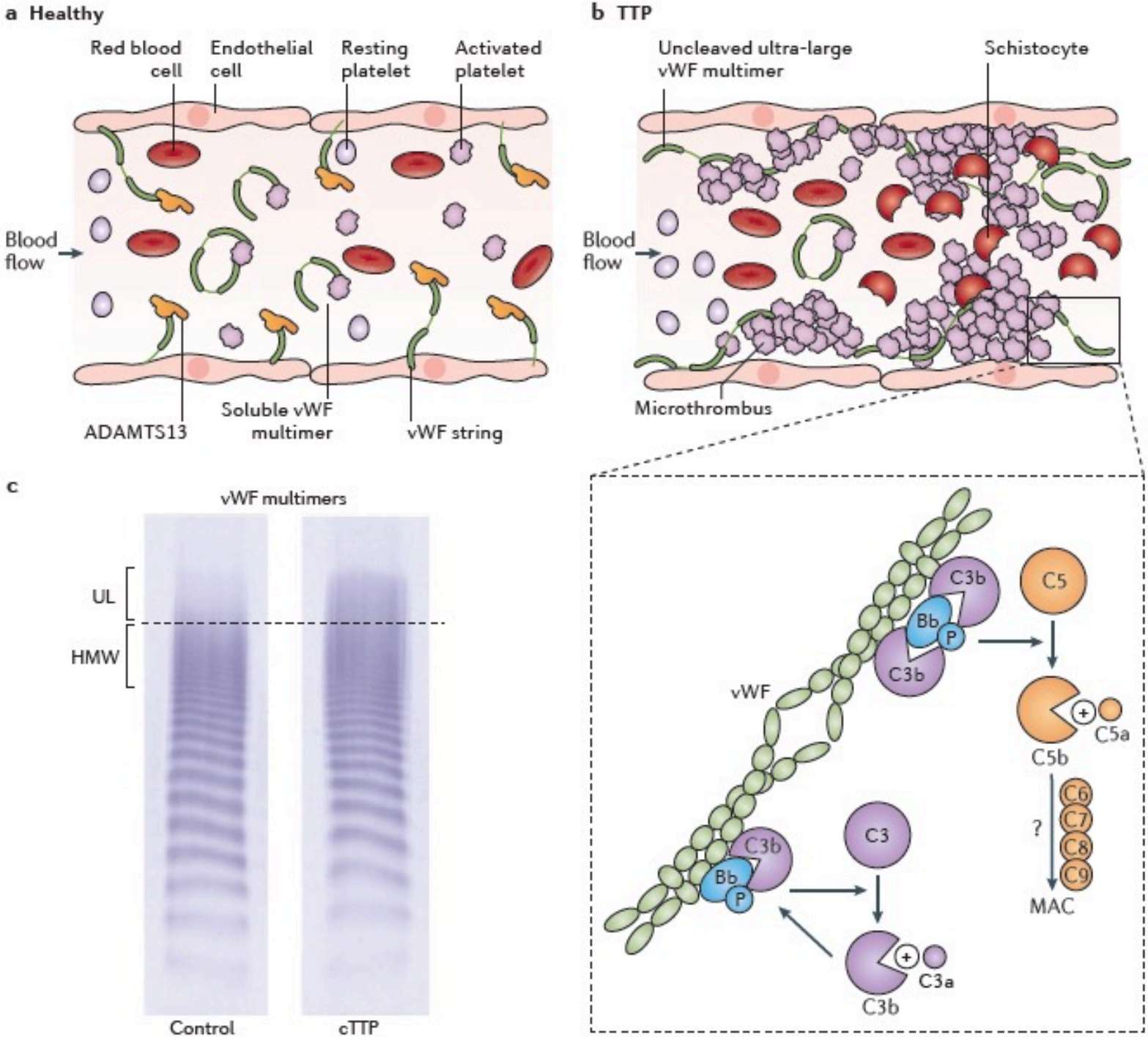
Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful; institutional review board [IRB] approval is desirable if apheresis treatment is undertaken in these circumstances

- Stiff person syndrome
- Hemolytic uremic syndrome (typical diarrhea-associated)
- Systemic lupus erythematosus (nephritis)
- Immune thrombocytopenia

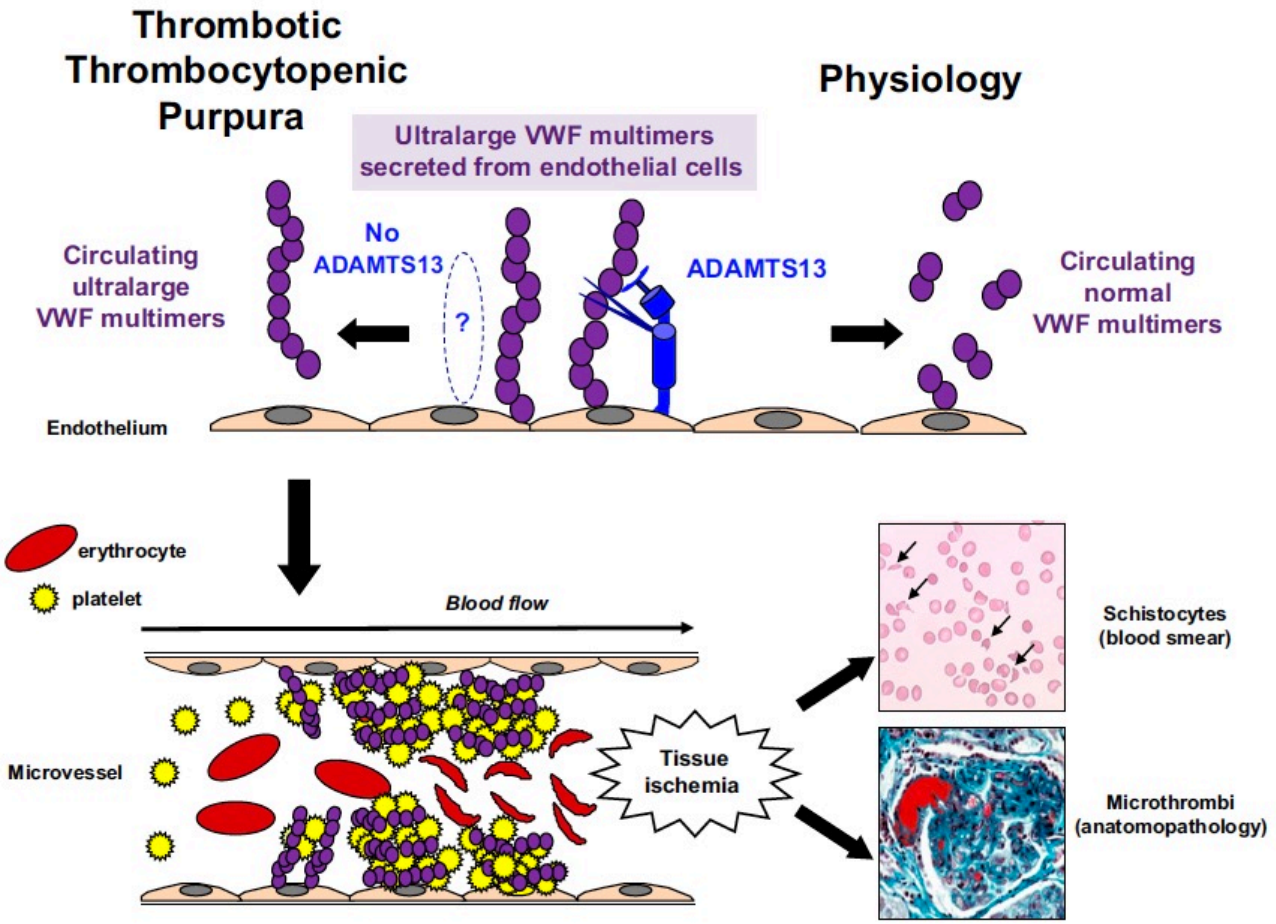
Thrombotic Thrombocytopenic Purpura

- TTP (TMA-ADAMTS 13 deficiency)
  - Classical pentad of diagnosis
    - Fever
    - Purpura or hemorrhage associated with thrombocytopenia
    - Microangiopathic hemolytic anemia (MAHA) with schistocytes on blood smear
    - Neurological manifestations
    - Variable degree of renal dysfunction
  - Current diagnosis: unexplained thrombocytopenia, MAHA
  - Associated with a severe (< 10%) deficiency of plasma ADAMTS 13 enzyme activity

Kremer Hovinga JA, Coppo P, Lämmle B, et al. Thrombotic thrombocytopenic purpura. Nat Rev Dis Primers 2017; 3: 17020


a Healthy
Red blood cell
Endothelial cell
Resting platelet
Activated platelet
Blood flow
ADAMTS13
Soluble vWF multimer
vWF string
b TTP
Uncleaved ultra-large vWF multimer
Schistocyte
Blood flow
Microthrombus
c
vWF multimers
UL
HMW
Control
cTTP
vWF
C3b
Bb
P
C5
C5a
C5b
C6
C7
C8
C9
MAC
?
C3
C3a

Pathophysiology of TTP



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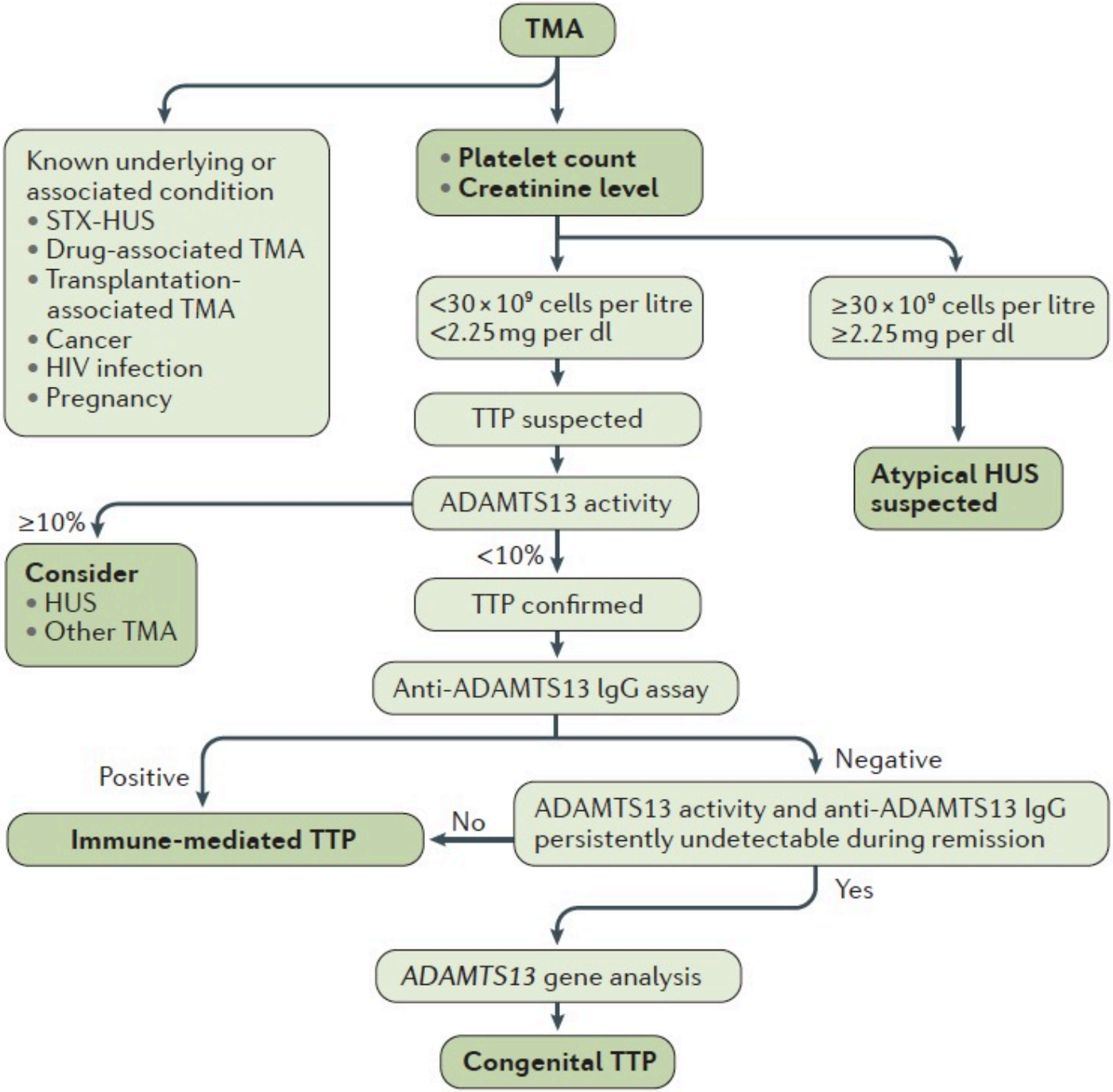
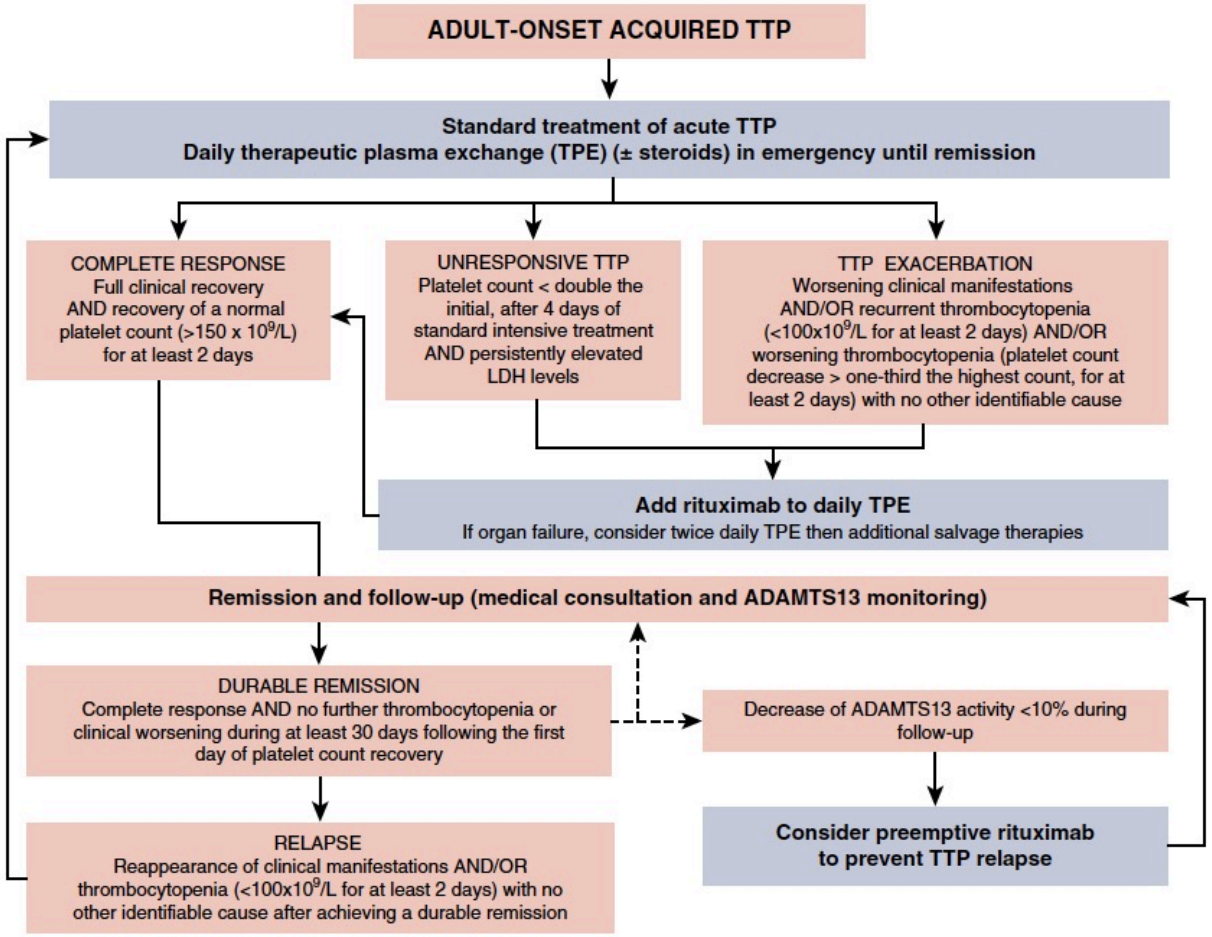

TMA
Known underlying or associated condition
• STX-HUS
• Drug-associated TMA
• Transplantation-associated TMA
• Cancer
• HIV infection
• Pregnancy
• Platelet count
• Creatinine level
<30 × 10⁹ cells per litre
<2.25 mg per dl
≥30 × 10⁹ cells per litre
≥2.25 mg per dl
TTP suspected
Atypical HUS suspected
ADAMTS13 activity
≥10%
Consider
• HUS
• Other TMA
<10%
TTP confirmed
Anti-ADAMTS13 IgG assay
Positive
Negative
Immune-mediated TTP
No
ADAMTS13 activity and anti-ADAMTS13 IgG persistently undetectable during remission
Yes
ADAMTS13 gene analysis
Congenital TTP

Treatment of TTP



Joly BS, Coppo P, Veyradier A. Thrombotic thrombocytopenic purpura. Blood 2017; 129: 2836-2846

TPE in the Management of TTP

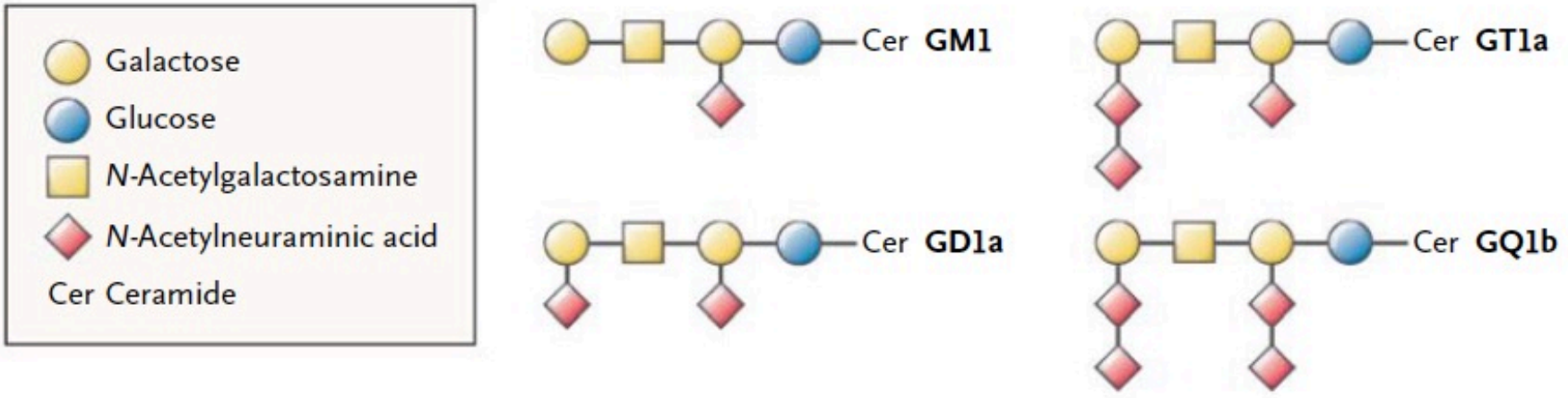
- Objective
  - Remove anti-ADAMTS13 autoantibodies
  - Replace missing ADAMTS13
- Technical notes
  - Volume treated: 1 – 1.5 TPV
  - Replacement fluid: plasma
  - Frequency: daily
- Criteria for discontinuation
  - Platelet count > 150 x 10^9/L and LDH near normal for 2 – 3 consecutive days

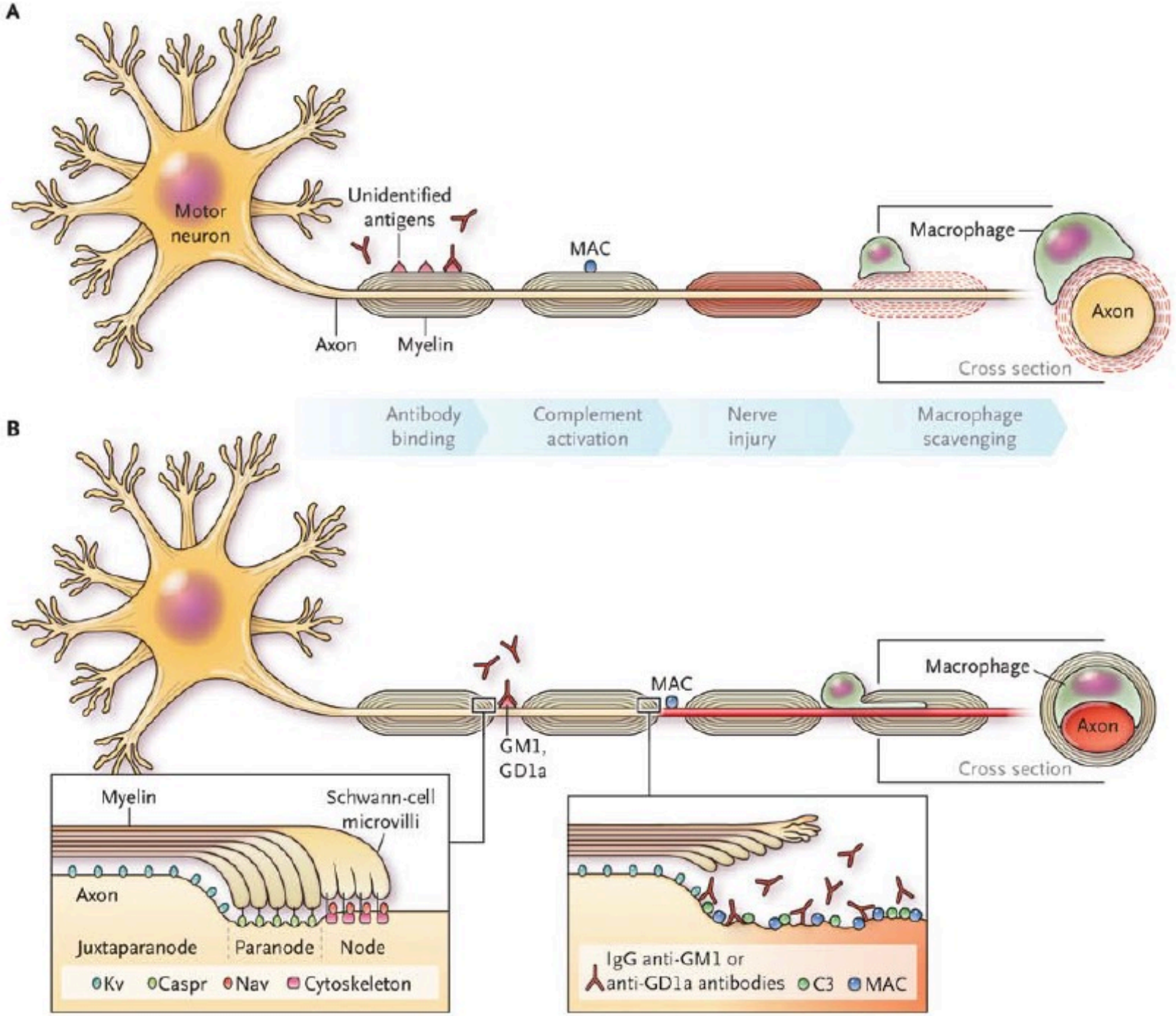
Schwartz J, Padmanabhan A, Aqui N, et al. Guidelines the use of therapeutic apheresis in clinical practice – Evidence-based approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue. J Clin Apheresis 2016; 31: 149-338
Kaplan AA. Therapeutic plasma exchange: core curriculum 2008. Am J Kidney Dis 2008; 52: 1180-1196

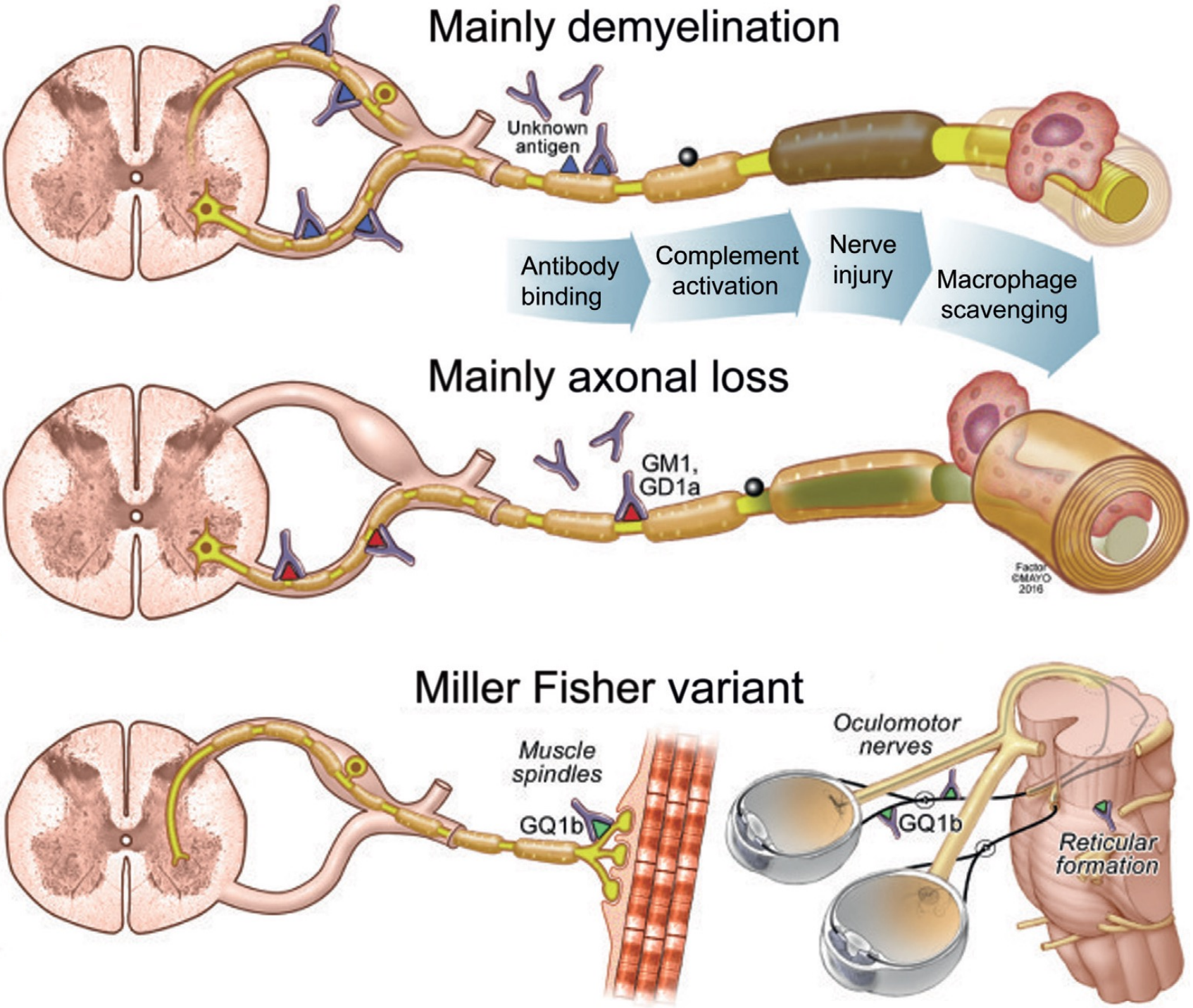
Guillain-Barré Syndrome

- Guillain-Barré Syndrome (GBS)
  - acute inflammatory demyelinating polyneuropathy (AIDP)
- Clinical manifestation
  - A prolonged, disabling neuromuscular disorder with respiratory difficulties in nearly a third of affected patients
- Pathological characteristics
  - An acute, monophasic, inflammatory, mostly demyelinating polyradiculoneuropathy
  - Primary-onset axonal varieties
- Incidence
  - 1.11 (0.89 to 1.89) cases per 100,000 person-years

Subtypes and variants	IgG autoantibodies to
Guillain–Barré syndrome	
Acute inflammatory demyelinating polyneuropathy	None
Facial variant: Facial diplegia and paresthesia	None
Acute motor axonal neuropathy	GM1, GD1a
More and less extensive forms	
Acute motor–sensory axonal neuropathy	GM1, GD1a
Acute motor-conduction-block neuropathy	GM1, GD1a
Pharyngeal–cervical–brachial weakness	GT1a > GQ1b >> GD1a
Miller Fisher syndrome	GQ1b, GT1a
Incomplete forms	
Acute ophthalmoparesis (without ataxia)	GQ1b, GT1a
Acute ataxic neuropathy (without ophthalmoplegia)	GQ1b, GT1a
CNS variant: Bickerstaff's brain-stem encephalitis	GQ1b, GT1a



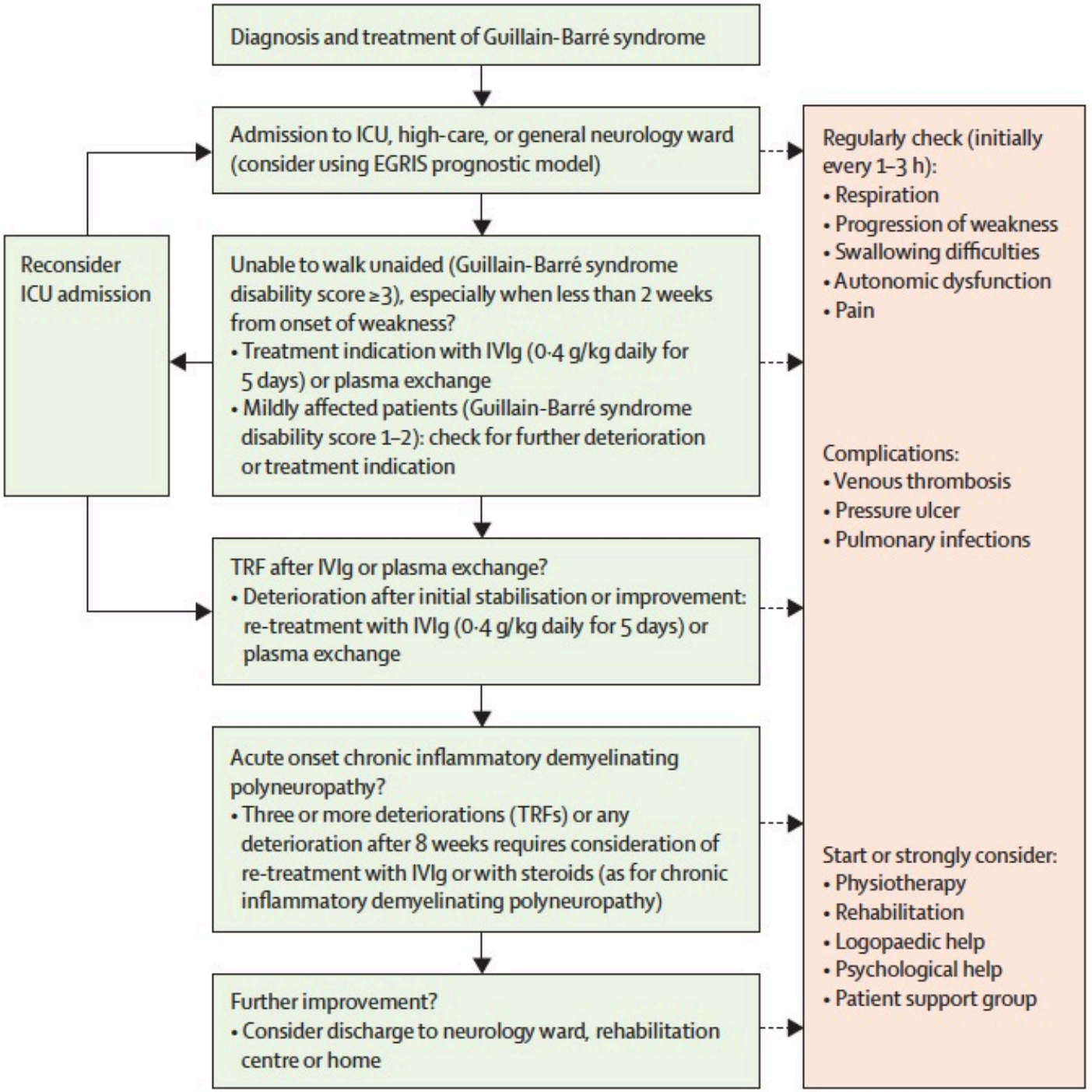

A
Motor neuron
Unidentified antigens
MAC
Macrophage
Axon
Axon
Myelin
Cross section
Antibody binding
Complement activation
Nerve injury
Macrophage scavenging
B
GM1, GD1a
MAC
Macrophage
Axon
Cross section
Myelin
Schwann-cell microvilli
Axon
Juxtaparanode
Paranode
Node
Kv
Caspr
Nav
Cytoskeleton
IgG anti-GM1 or anti-GD1a antibodies
C3
MAC


Mainly demyelination
Unknown antigen
Antibody binding
Complement activation
Nerve injury
Macrophage scavenging
Mainly axonal loss
GM1, GD1a
Miller Fisher variant
Muscle spindles
GQ1b
Oculomotor nerves
GQ1b
Reticular formation

Diagnosis of Guillain-Barré Syndrome

- **Features needed for diagnosis of GBS in clinical practice**
  Progressive weakness in legs and arms (sometimes initially only in legs); Areflexia (or decreased tendon reflexes) in weak limbs
- **Additional symptoms** Progressive phase lasts days to 4 weeks (often 2 weeks); Relative symmetry; Mild sensory symptoms or signs (not present in acute motor axonal neuropathy); Cranial nerve involvement, especially bilateral weakness of facial muscles; Autonomic dysfunction; Pain(common).
- **Features that should raise doubt about the diagnosis of GBS** CSF: increased number of mononuclear cells or polymorphonuclear cells (>50 cells per µL); Severe pulmonary dysfunction with little or no limb weakness at onset; Severe sensory signs with little or no weakness at onset; Bladder or bowel dysfunction at onset; Fever at onset; Sharp spinal cord sensory level; Marked, persistent asymmetry of weakness; Persistent bladder or bowel dysfunction; Slow progression of weakness and without respiratory involvement (consider subacute inflammatory demyelinating polyneuropathy or acute onset chronic inflammatory demyelinating polyneuropathy)
- **Nerve conduction studies** Can be helpful in clinical practice, but are generally not required to diagnose Guillain-Barré syndrome; Needed to meet all Brighton criteria for Guillain-Barré syndrome; Essential for classification of Guillain-Barré syndrome in acute inflammatory demyelinating polyneuropathy or acute motor axonal neuropathy; Acute inflammatory demyelinating polyneuropathy: features of demyelination (decreased motor nerve conduction velocity, prolonged distal motor latency, increased F-wave latency, conduction blocks, and temporal dispersion); Acute motor axonal neuropathy: no features of demyelination (one demyelinating feature in one nerve, if distal CMAP amplitude is less than 10% LLN, can be found; distal CMAP amplitude less than 80% LLN in at least two nerves. Transient motor nerve conduction block might be present

Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. Lancet 2016; 388: 717-727


Diagnosis and treatment of Guillain-Barré syndrome
Admission to ICU, high-care, or general neurology ward (consider using EGRIS prognostic model)
Reconsider ICU admission
Unable to walk unaided (Guillain-Barré syndrome disability score ≥3), especially when less than 2 weeks from onset of weakness?
• Treatment indication with IVIg (0·4 g/kg daily for 5 days) or plasma exchange
• Mildly affected patients (Guillain-Barré syndrome disability score 1–2): check for further deterioration or treatment indication
TRF after IVIg or plasma exchange?
• Deterioration after initial stabilisation or improvement: re-treatment with IVIg (0·4 g/kg daily for 5 days) or plasma exchange
Acute onset chronic inflammatory demyelinating polyneuropathy?
• Three or more deteriorations (TRFs) or any deterioration after 8 weeks requires consideration of re-treatment with IVIg or with steroids (as for chronic inflammatory demyelinating polyneuropathy)
Further improvement?
• Consider discharge to neurology ward, rehabilitation centre or home
Regularly check (initially every 1–3 h):
• Respiration
• Progression of weakness
• Swallowing difficulties
• Autonomic dysfunction
• Pain
Complications:
• Venous thrombosis
• Pressure ulcer
• Pulmonary infections
Start or strongly consider:
• Physiotherapy
• Rehabilitation
• Logopaedic help
• Psychological help
• Patient support group

TPE in Guillain Barré Syndrome

- Objective
  - Nonspecific removal of antibodies and complement
- Technical notes
  - Volume treated: 1 – 1.5 TPV
  - Replacement fluid: albumin
  - Frequency: every other day
- Criteria for discontinuation
  - Processing 200 – 250 ml/kg of plasma over 10 – 14 days (equivalent to 5 – 6 TPE procedures)

Yuki N, Hartung H. Guillain-Barré syndrome. N Engl J Med 2012; 366: 2294-2304

Myasthenia Gravis

- Epidemiology
  - Incidence: 8 to 10 cases per 1,000,000 persons per year
  - Prevalence: 150 to 250 cases per 1,000,000 population
- Pathogenesis
  - An autoimmune disease in which antibodies bind to acetylcholine receptors or to functionally related molecules in the postsynaptic membrane at the neuromuscular junction
- Clinical manifestation
  - Weakness of skeletal muscles (usu. symmetric, apart from the eye involvement)

Gilhus NE. Myasthenia gravis. N Engl J Med 2016; 375: 2570-2581

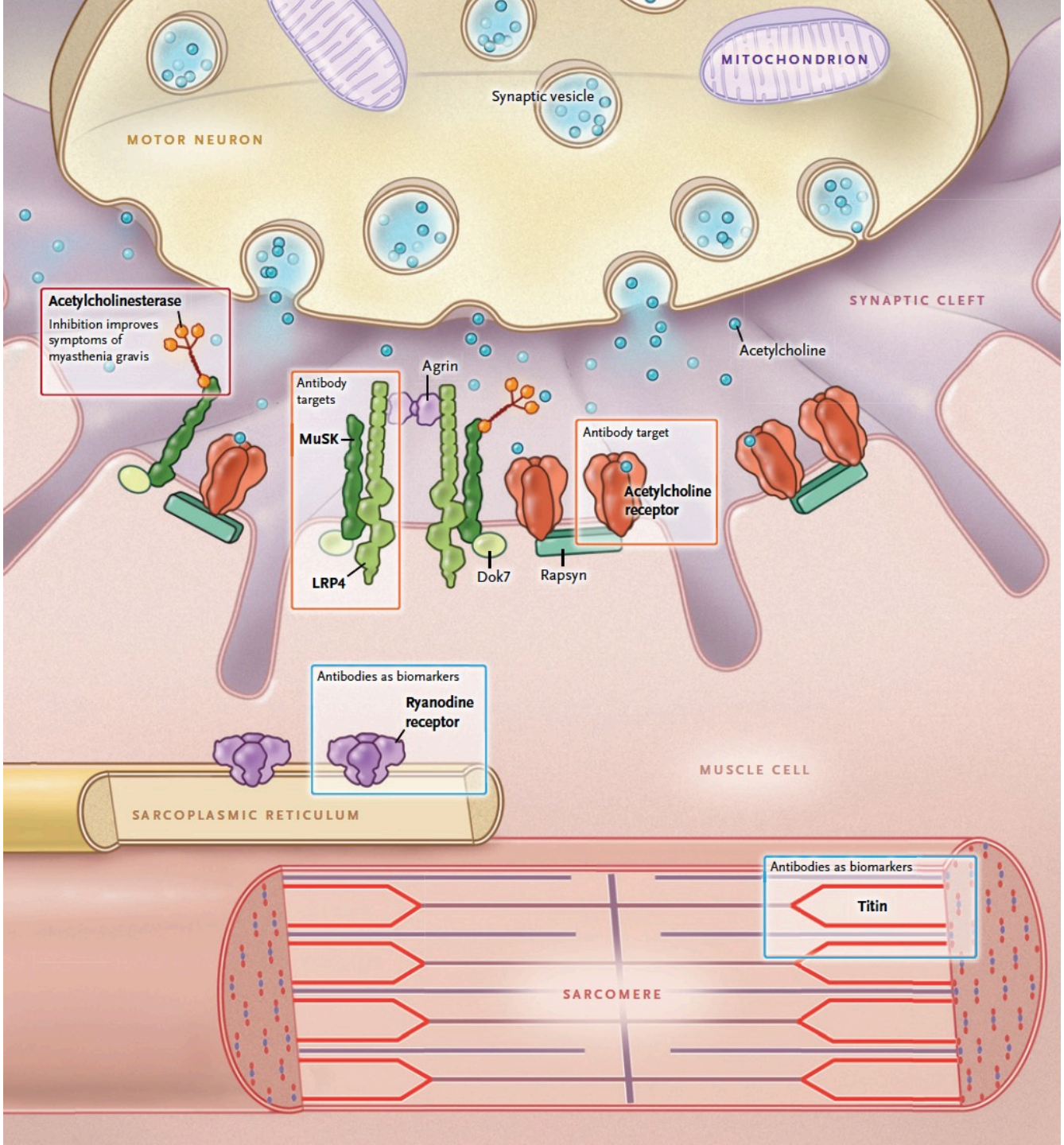
Pathogenesis of Myasthenia Gravis

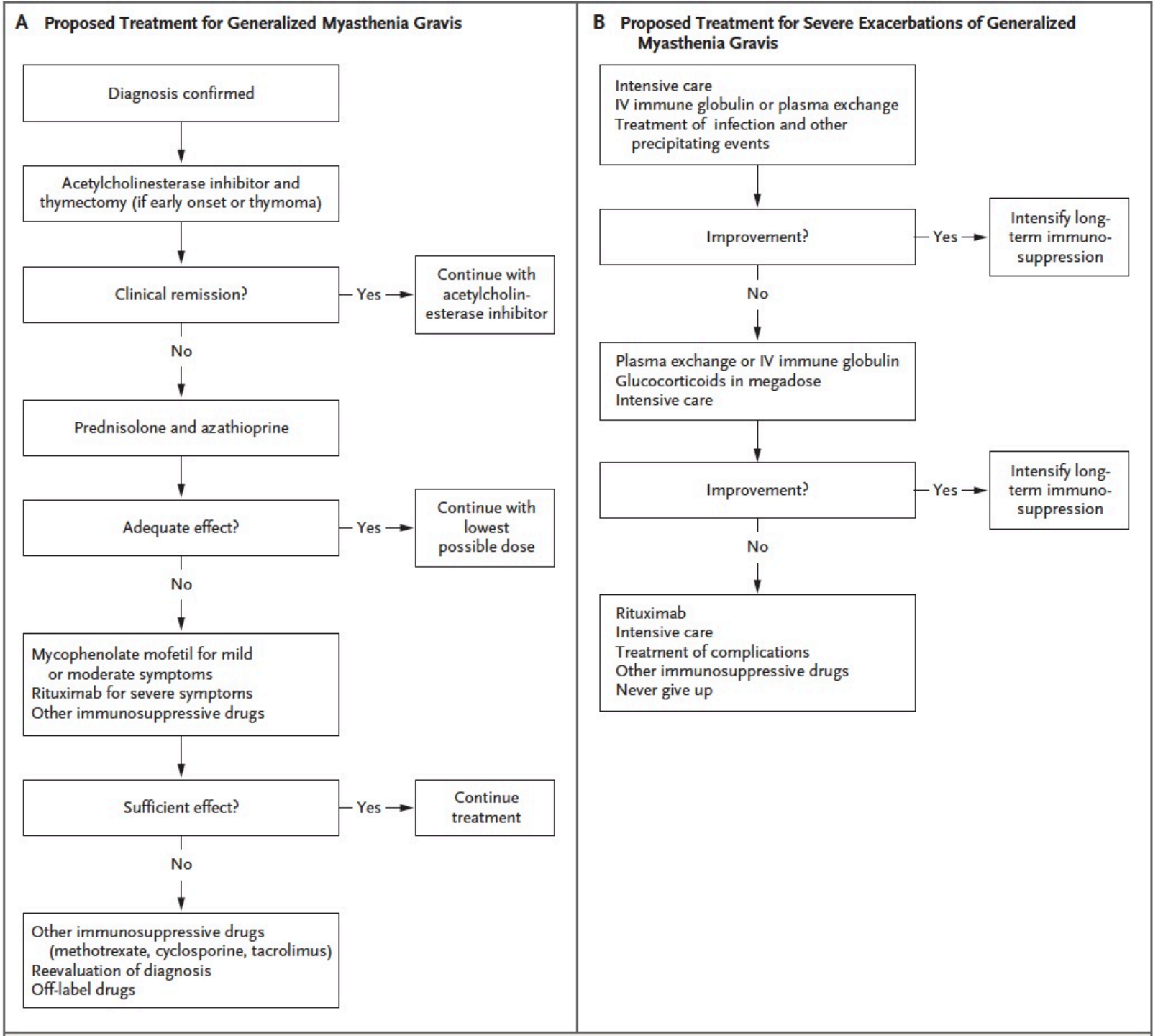
Table 1. Features of Myasthenia Gravis Subgroups.*

Subgroup	Antibody	Age at Onset	Thymus
Early onset	Acetylcholine receptor	<50 yr	Hyperplasia common
Late onset	Acetylcholine receptor	≥50 yr	Atrophy common
Thymoma	Acetylcholine receptor	Any age	Lymphoepithelioma
Muscle-specific kinase	Muscle-specific kinase	Any age	Normal
LRP4	LRP4	Any age	Normal
Seronegative	None detected	Any age	Variable
Ocular	Variable	Any age	Variable

* LRP4 denotes lipoprotein receptor–related protein 4.

Gilhus NE. Myasthenia gravis. N Engl J Med 2016; 375: 2570-2581


MITOCHONDRION
Synaptic vesicle
MOTOR NEURON
Acetylcholinesterase
Inhibition improves symptoms of myasthenia gravis
SYNAPTIC CLEFT
Acetylcholine
Antibody targets
MuSK
LRP4
Agrin
Dok7
Rapsyn
Antibody target
Acetylcholine receptor
Antibodies as biomarkers
Ryanodine receptor
MUSCLE CELL
SARCOPLASMIC RETICULUM
Antibodies as biomarkers
Titin
SARCOMERE


A Proposed Treatment for Generalized Myasthenia Gravis
Diagnosis confirmed
Acetylcholinesterase inhibitor and thymectomy (if early onset or thymoma)
Clinical remission?
Yes
Continue with acetylcholin-esterase inhibitor
No
Prednisolone and azathioprine
Adequate effect?
Yes
Continue with lowest possible dose
No
Mycophenolate mofetil for mild or moderate symptoms
Rituximab for severe symptoms
Other immunosuppressive drugs
Sufficient effect?
Yes
Continue treatment
No
Other immunosuppressive drugs (methotrexate, cyclosporine, tacrolimus)
Reevaluation of diagnosis
Off-label drugs
B Proposed Treatment for Severe Exacerbations of Generalized Myasthenia Gravis
Intensive care
IV immune globulin or plasma exchange
Treatment of infection and other precipitating events
Improvement?
Yes
Intensify long-term immuno-suppression
No
Plasma exchange or IV immune globulin
Glucocorticoids in megadose
Intensive care
Improvement?
Yes
Intensify long-term immuno-suppression
No
Rituximab
Intensive care
Treatment of complications
Other immunosuppressive drugs
Never give up

TPE in Myasthenia Gravis

- Objective
  - Removal of circulating autoantibodies, particularly in myasthenia crisis, perioperatively for thymectomy, or as an adjunct to other therapies to maintain optimal clinical status
- Technical notes
  - Volume treated: 1 – 1.5 TPV
  - Replacement fluid: albumin
  - Frequency: daily or every other day
- Criteria for discontinuation
  - Typical induction regimen consisting of processing 225 ml/kg of plasma over a period of up to 2 weeks

Schwartz J, Padmanabhan A, Aqui N, et al. Guidelines the use of therapeutic apheresis in clinical practice – Evidence-based approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue. J Clin Apheresis 2016; 31: 149-338

Indications for Urgent TPE

Pathology	Category	Grade of Recommendation
Thrombotic thrombocytopenic purpura	I	1A
Catastrophic antiphspholipid syndrome	II	2C
Acute pancreatitis due to hypertriglyceridemia	III	1B
Intoxication by drugs or poisoning	II/III	2C
Hyperviscosity syndromes	I	1B
Acute fulminating hepatitis	III	2B
Acute inflammatory demyelinating polyneuropathy	I	1A
Myasthenia gravis	I	1A

Russi G, Marson P. Urgent plasma exchange: how, where and when. Blood Transfus 2011; 9: 356-361

Effectiveness of TPE

- Volume of plasma removed relative to total plasma volume
- Distribution of substance to be removed
  - Between intra and extravascular compartments
- Speed at which the substance equilibrates between compartments
- Rate at which then substance is synthesized

What Do You Want to Remove in Sepsis and/or Septic Shock?

Inflammatory cytokines mainly distributed in the intravascular compartment?

Proinflammatory Cytokines in Sepsis

Table 3. Molecular weight, sieving coefficients and endogenous half-lives of some cytokines

Cytokines	Molecular weight	Sieving coefficient	Half-life *minutes*
TNFα	~17.4	0–0.2,[a] 0.01–1.0 [52]	~6–7 [45] ~14–17 [43]
monomer			~15 [47]
trimer	~52		
IL-1	~18	0.07–0.42,[b] 0.35 [38] 0.18 [39], 0.12–1.0 [52]	~6–10 [44]
IL-2			~6–10 [46]
IL-6	~26	0.01–0.32 [52]	~6 [49]
IL-8	~6–8	0.0–0.48,[b] 0.44 [39]	

[a] Data are from the literature [10]
[b] Rising sieving coefficient during hemofiltration

Sieberth H, Kierdorf HP. Is cytokine removal by continuous hemofiltration feasible? Kidney Intl 1999; 56(Suppl72): S79-S83

TPE in Sepsis and Septic Shock

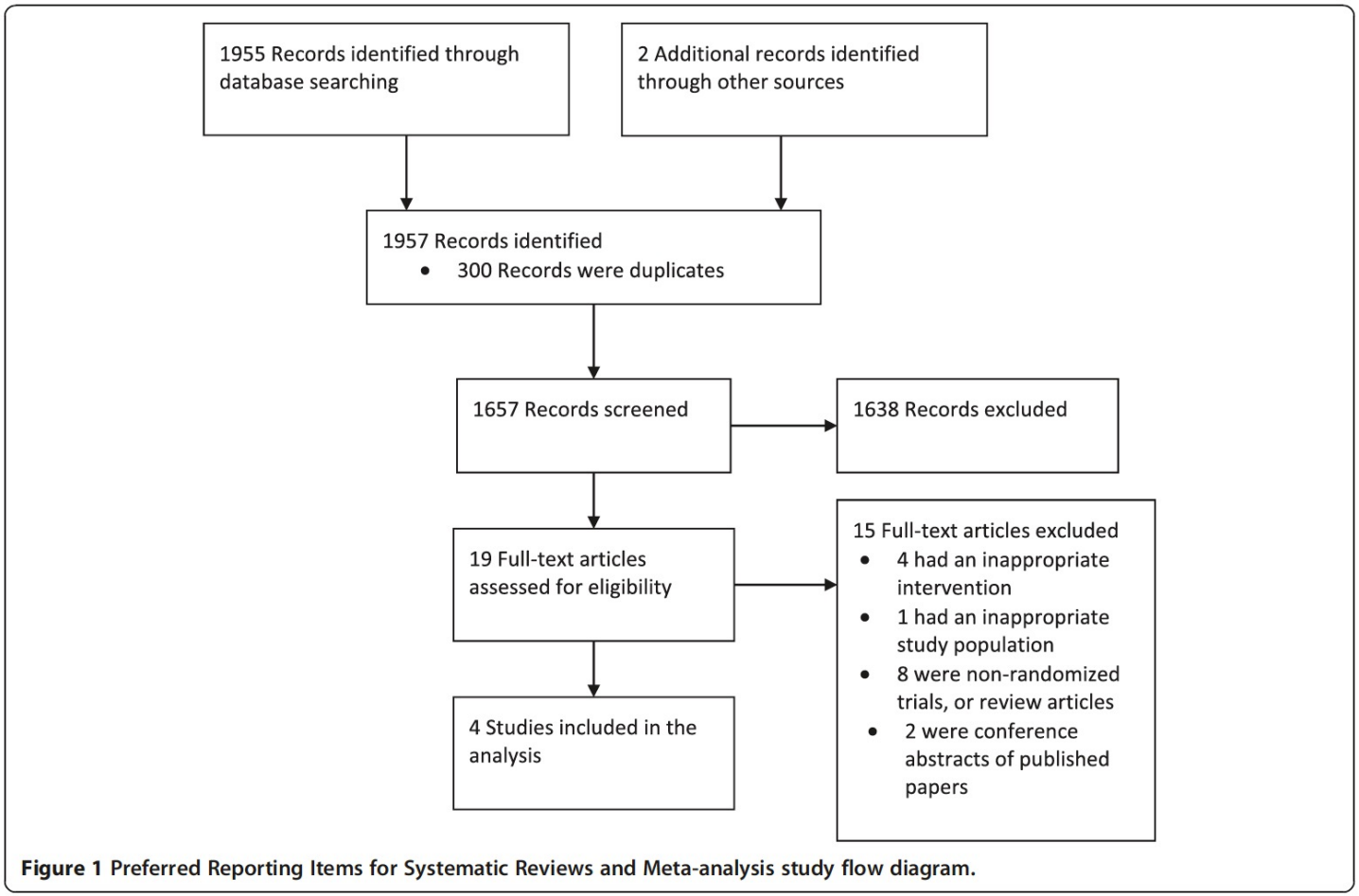


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-analysis study flow diagram.

Rimmer E, Houston BL, Kumar A, et al. The efficacy and safety of plasma exchange in patients with sepsis and septic shock: a systematic review and meta-analysis. Crit Care 2014; 18: 699

TPE in Sepsis and Septic Shock

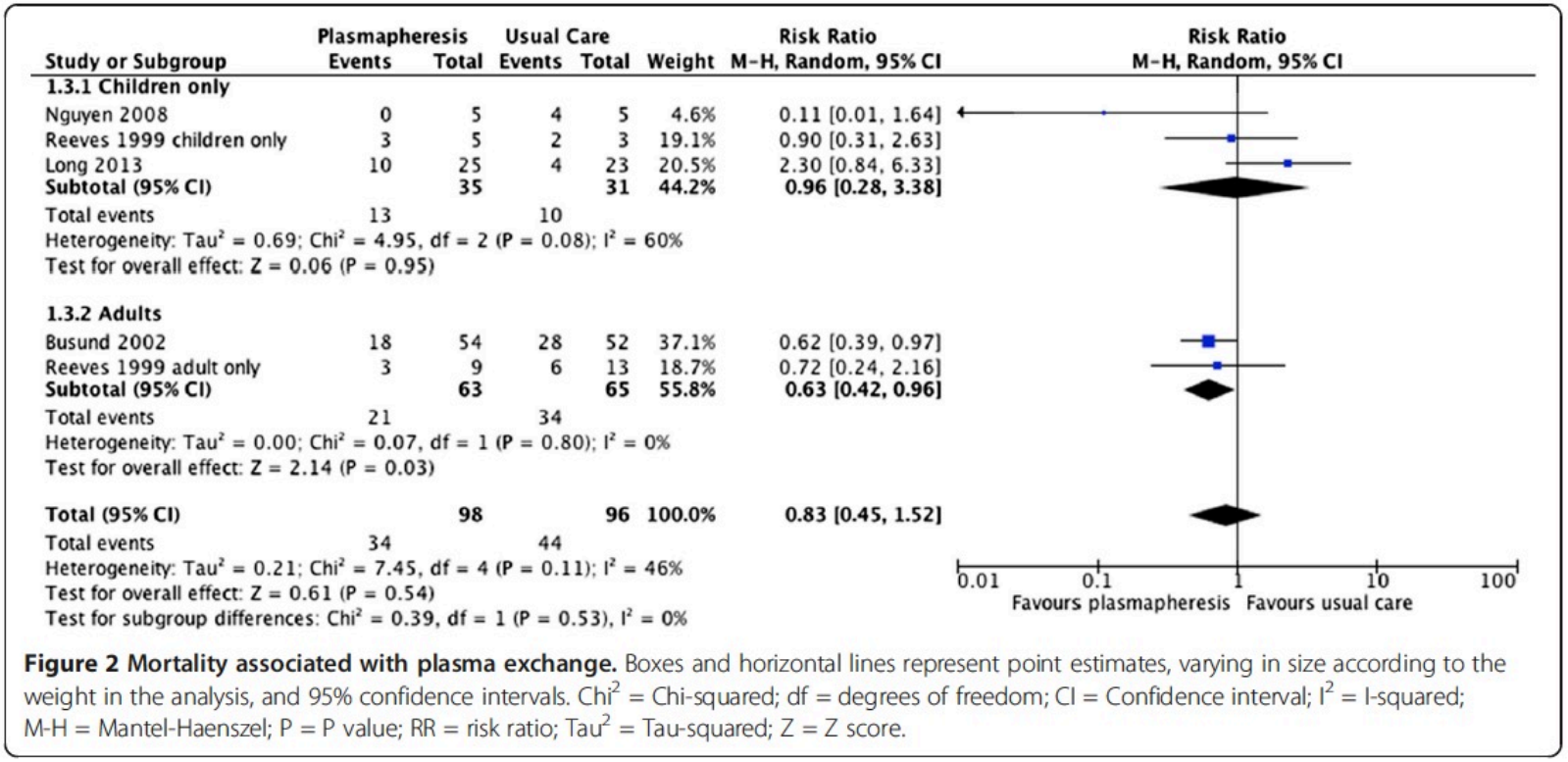


Figure 2 Mortality associated with plasma exchange. Boxes and horizontal lines represent point estimates, varying in size according to the weight in the analysis, and 95% confidence intervals. Chi^2 = Chi-squared; df = degrees of freedom; CI = Confidence interval; I^2 = I-squared; M-H = Mantel-Haenszel; P = P value; RR = risk ratio; Tau^2 = Tau-squared; Z = Z score.

Rimmer E, Houston BL, Kumar A, et al. The efficacy and safety of plasma exchange in patients with sepsis and septic shock: a systematic review and meta-analysis. Crit Care 2014; 18: 699

Take Home Message

- Therapeutic plasma exchange as an important definitive therapy in some, but not all, critically ill patients
- Well established indication in some rheumatic/renal/neurological diseases and/or clinical syndromes
- Currently not indicated in the management of sepsis/septic shock