Therapeutic Plasmaexchange
few answers and many question

Jan T Kielstein
Medical Clinic V | Nephrology – Rheumatology – Blood Purification
Academic Teaching Hospital Braunschweig | GERMANY

Therapeutic Plasmaexchange
few answers and many question

1) **Who should be treated?**

2) **Which device should we use?**

3) **How to define treatment dose?**

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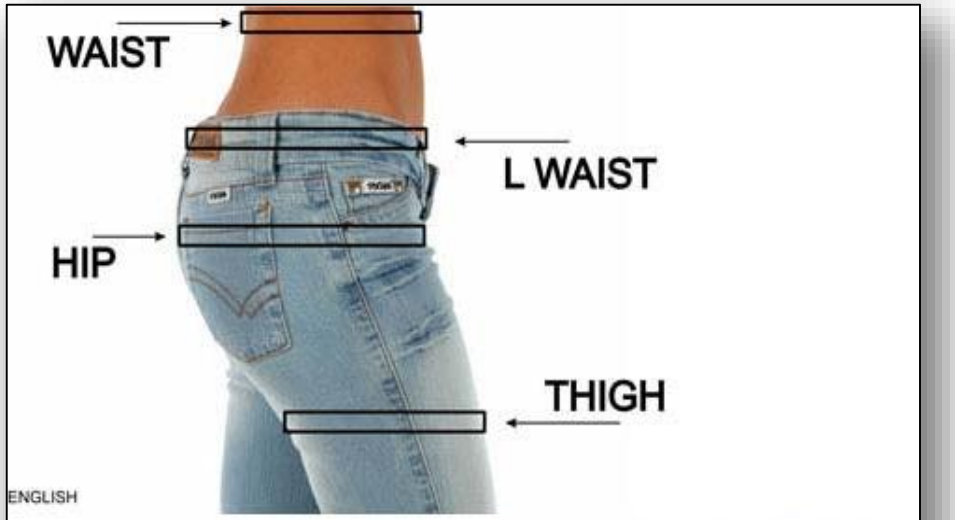
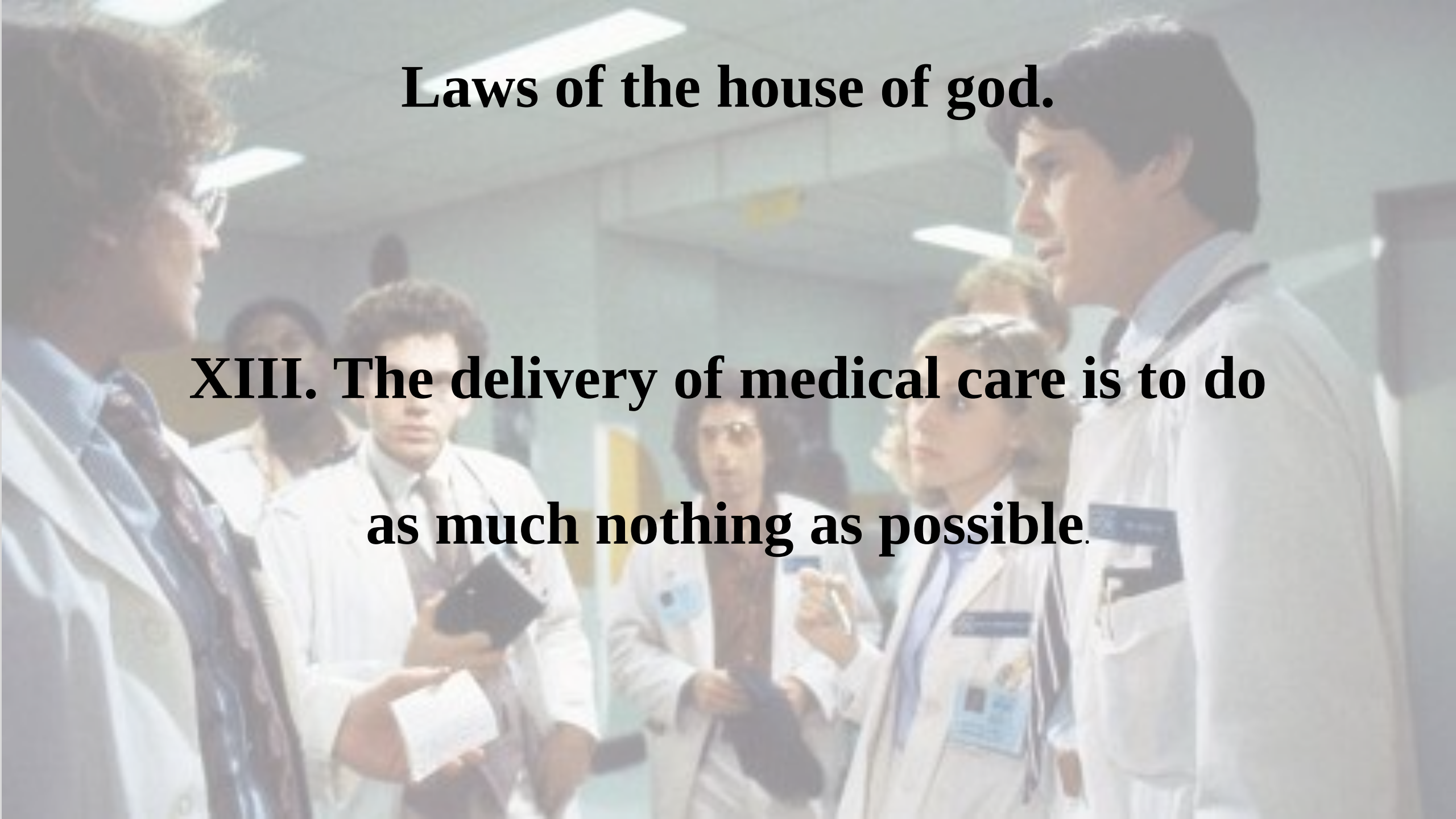


DJW CHART IS ONLY A REFERENCE TO HELP YOU CHOOSE YOUR SIZE

SIZE	HIP	WAIST
0	HIP 32" 33"	24-25
1	HIP 34" 35"	25-26
3	HIP 36" 37"	26-28
5	HIP 38" 39"	28-30
7	HIP 40" 41"	30-32
9	HIP 41" 42"	32-33
11	HIP 43" 44"	33-34



Laws of the house of god.

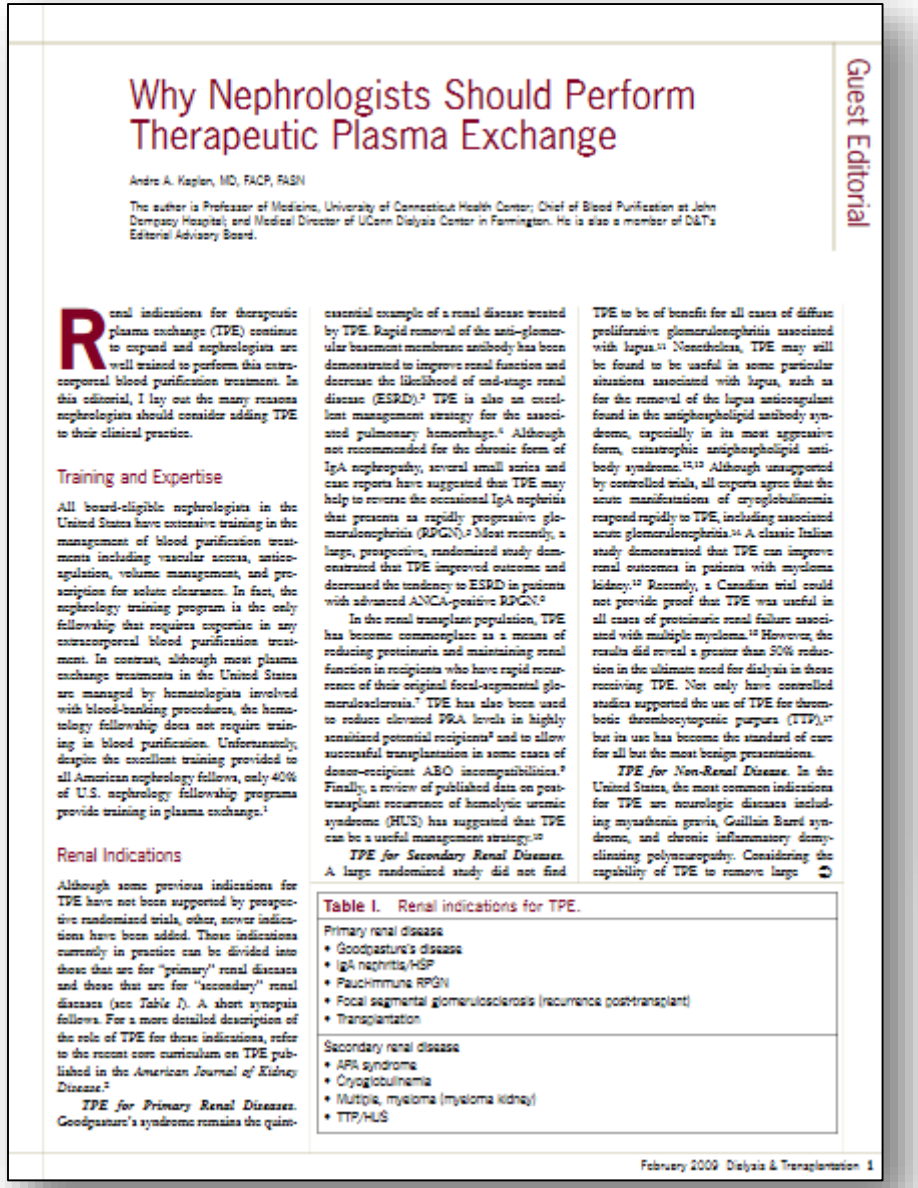
XIII. The delivery of medical care is to do as much nothing as possible.

Andre A. Kaplan

“Nobody in the ICU should die without plasma exchange”

Klinikum Braunschweig

Why nephrologists should perform therapeutic plasma exchange



Guest Editorial

Why Nephrologists Should Perform Therapeutic Plasma Exchange

Andre A. Kaplan, MD, FACP, FASN

The author is Professor of Medicine, University of Connecticut Health Center; Chief of Blood Purification at John Dempsey Hospital; and Medical Director of UConn Dialysis Center in Farmington. He is also a member of D&T's Editorial Advisory Board.

Renal indications for therapeutic plasma exchange (TPE) continue to expand and nephrologists are well trained to perform this extracorporeal blood purification treatment. In this editorial, I lay out the many reasons nephrologists should consider adding TPE to their clinical practice.

Training and Expertise

All board-eligible nephrologists in the United States have extensive training in the management of blood purification treatments including vascular access, anticoagulation, volume management, and prescription for solute clearance. In fact, the nephrology training program is the only fellowship that requires expertise in any extracorporeal blood purification treatment. In contrast, although most plasma exchange treatments in the United States are managed by hematologists involved with blood-banking procedures, the hematology fellowship does not require training in blood purification. Unfortunately, despite the excellent training provided to all American nephrology fellows, only 40% of U.S. nephrology fellowship programs provide training in plasma exchange.[1]

Renal Indications

Although some previous indications for TPE have not been supported by prospective randomized trials, other, newer indications have been added. These indications currently in practice can be divided into those that are for "primary" renal diseases and those that are for "secondary" renal diseases (see *Table I*). A short synopsis follows. For a more detailed description of the role of TPE for these indications, refer to the recent core curriculum on TPE published in the *American Journal of Kidney Disease*.[2]

TPE for Primary Renal Diseases. Goodpasture's syndrome remains the quintessential example of a renal disease treated by TPE. Rapid removal of the anti–glomerular basement membrane antibody has been demonstrated to improve renal function and decrease the likelihood of end-stage renal disease (ESRD).[3] TPE is also an excellent management strategy for the associated pulmonary hemorrhage.[4] Although not recommended for the chronic form of IgA nephropathy, several small series and case reports have suggested that TPE may help to reverse the occasional IgA nephritis that presents as rapidly progressive glomerulonephritis (RPGN).[5] Most recently, a large, prospective, randomized study demonstrated that TPE improved outcome and decreased the tendency to ESRD in patients with advanced ANCA-positive RPGN.[6]

In the renal transplant population, TPE has become commonplace as a means of reducing proteinuria and maintaining renal function in recipients who have rapid recurrence of their original focal-segmental glomerulosclerosis.[7] TPE has also been used to reduce elevated PRA levels in highly sensitized potential recipients[8] and to allow successful transplantation in some cases of donor-recipient ABO incompatibilities.[9] Finally, a review of published data on post-transplant recurrence of hemolytic uremic syndrome (HUS) has suggested that TPE can be a useful management strategy.[10]

TPE for Secondary Renal Diseases. A large randomized study did not find TPE to be of benefit for all cases of diffuse proliferative glomerulonephritis associated with lupus.[11] Nonetheless, TPE may still be found to be useful in some particular situations associated with lupus, such as for the removal of the lupus anticoagulant found in the antiphospholipid antibody syndrome, especially in its most aggressive form, catastrophic antiphospholipid antibody syndrome.[12,13] Although unsupported by controlled trials, all experts agree that the acute manifestations of cryoglobulinemia respond rapidly to TPE, including associated acute glomerulonephritis.[14] A classic Italian study demonstrated that TPE can improve renal outcomes in patients with myeloma kidney.[15] Recently, a Canadian trial could not provide proof that TPE was useful in all cases of proteinuric renal failure associated with multiple myeloma.[16] However, the results did reveal a greater than 50% reduction in the ultimate need for dialysis in those receiving TPE. Not only have controlled studies supported the use of TPE for thrombotic thrombocytopenic purpura (TTP),[17] but its use has become the standard of care for all but the most benign presentations.

TPE for Non-Renal Disease. In the United States, the most common indications for TPE are neurologic diseases including myasthenia gravis, Guillain Barré syndrome, and chronic inflammatory demyelinating polyneuropathy. Considering the capability of TPE to remove large ➲

Table I. Renal indications for TPE.

Primary renal disease
• Goodpasture's disease
• IgA nephritis/HSP
• Pauci-immune RPGN
• Focal segmental glomerulosclerosis (recurrence post-transplant)
• Transplantation
Secondary renal disease
• APA syndrome
• Cryoglobulinemia
• Multiple, myeloma (myeloma kidney)
• TTP/HUS

Table I. Renal indications for TPE.

Primary renal disease
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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

Disease name	TA Modality	Indication	Category	Grade	Page
Atopic (neuro-) dermatitis (atopic eczema), recalcitrant	ECP		III	2C	179
	IA		III	2C	
	TPE		III	2C	
Coagulation factor inhibitors	TPE	Alloantibody	IV	2C	197
	TPE	Autoantibody	III	2C	
	IA	Alloantibody	III	2B	
	IA	Autoantibody	III	1C	
Complex regional pain syndrome	TPE	Chronic	III	2C	199
Cryoglobulinemia	TPE	Symptomatic/severe	II	2A	201
	IA	Symptomatic/severe	II	2B	
Dilated cardiomyopathy, idiopathic	IA	NYHA II-IV	II	1B	207
	TPE	NYHA II-IV	III	2C	
Multiple sclerosis	TPE	Acute CNS inflammatory demyelinating	II	1B	257
	IA	Acute CNS inflammatory demyelinating	III	2C	
	TPE	Chronic progressive	III	2B	
Renal transplantation, ABO compatible	TPE/IA	Antibody mediated rejection	I	1B	297
	TPE/IA	Desensitization, LD	I	1B	
	TPE/IA	Desensitization, DD	III	2C	
Renal transplantation, ABO incompatible	TPE/IA	Desensitization, LD	I	1B	299
	TPE/IA	Antibody medicated rejection	II	1B	

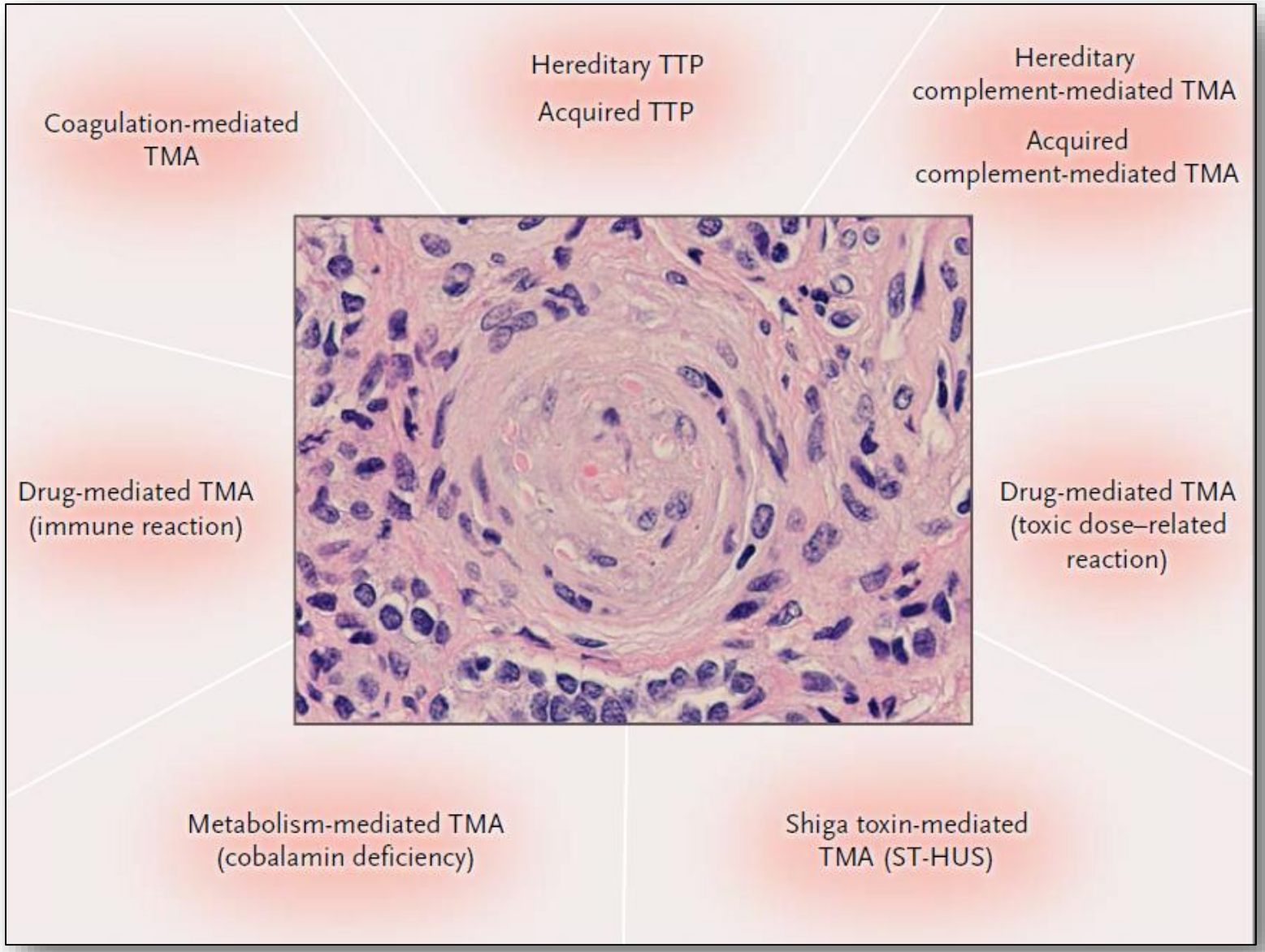
SCHWARTZ et al. Journal of Clinical Apheresis 31:149–162, 2016

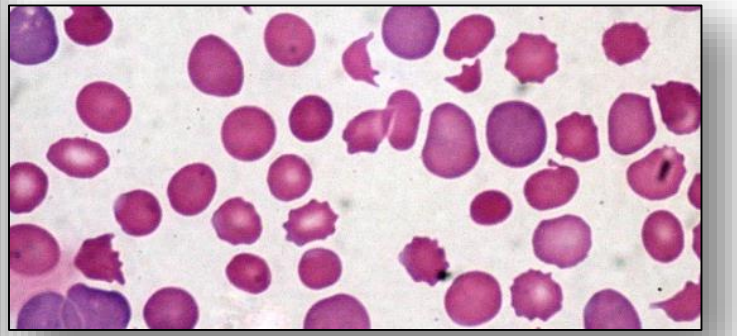
Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue

Disease name	TA Modality	Indication	Category	Grade	Page
Paraneoplastic neurological syndromes	TPE		III	2C	271
	IA		III	2C	
Paraproteinemic demyelinating neuropathies/chronic acquired demyelinating polyneuropathies	TPE	Anti-MAG neuropathy	III	1C	273
	TPE	Multifocal Motor Neuropathy	IV	1C	
	TPE	IgG/IgA	I	1B	
	TPE	IgM	I	1C	
	TPE	Multiple myeloma	III	2C	
	IA	IgG/IgA/IgM	III	2C	
Pemphigus vulgaris	TPE	Severe	III	2B	277
	ECP	Severe	III	2C	
	IA	Severe	III	2C	
Thrombotic microangiopathy, Shiga toxin mediated	TPE/IA	Severe neurological symptoms	III	2C	325
	TPE	Streptococcus pneumoniae	III	2C	
	TPE	Absence of severe neurological symptoms	IV	1C	

SCHWARTZ et al. Journal of Clinical Apheresis 31:149–162, 2016

Syndromes of Thrombotic Microangiopathy

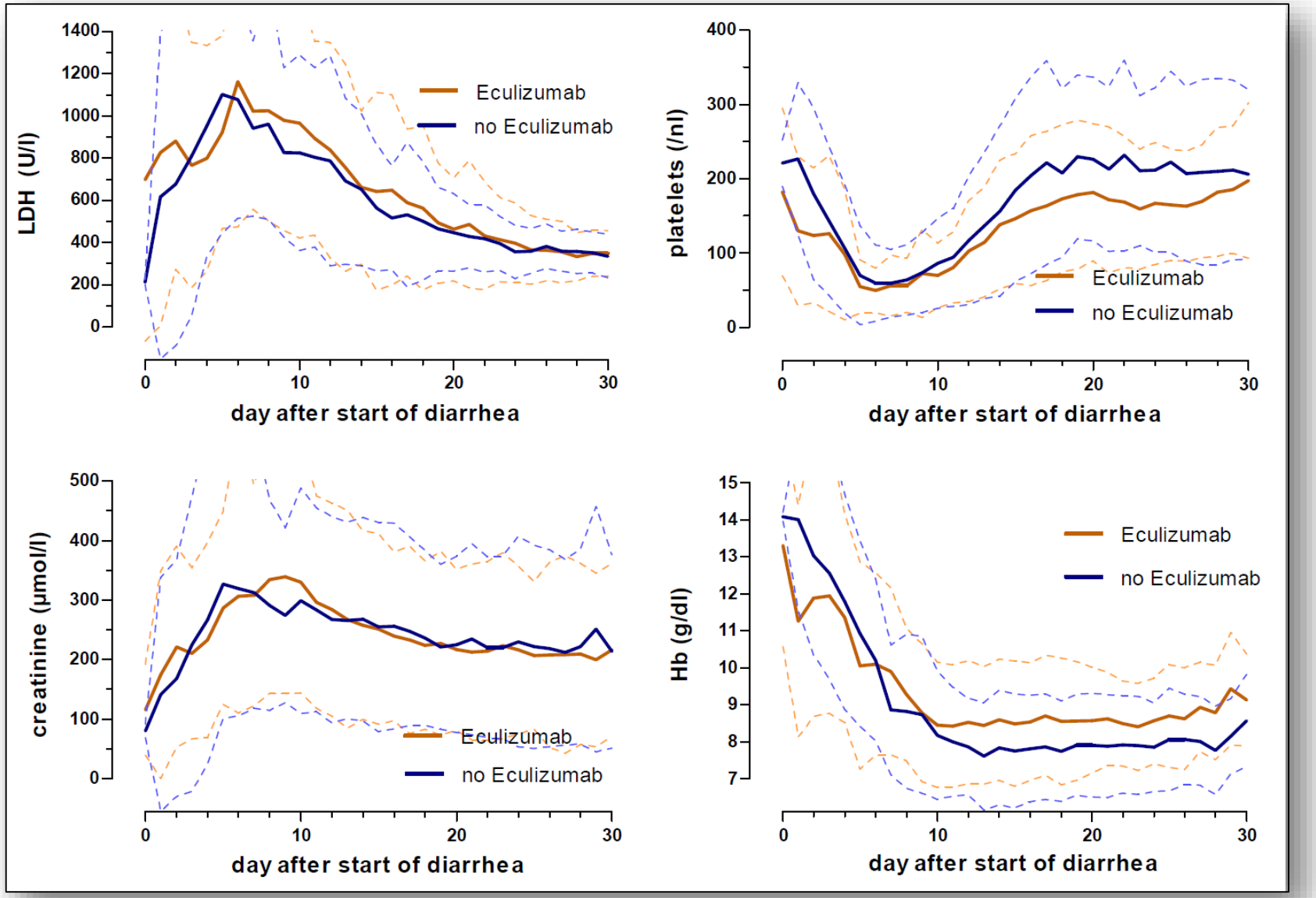




GEORGE&NESTER
N Engl J Med 371:654-66, 2014

Klinikum Braunschweig

Validation of treatment strategies for enterohaemorrhagic Escherichia coli O104:H4 induced HUS: case-control study.



MENNE et al.
BMJ ;345:e4565, 2012

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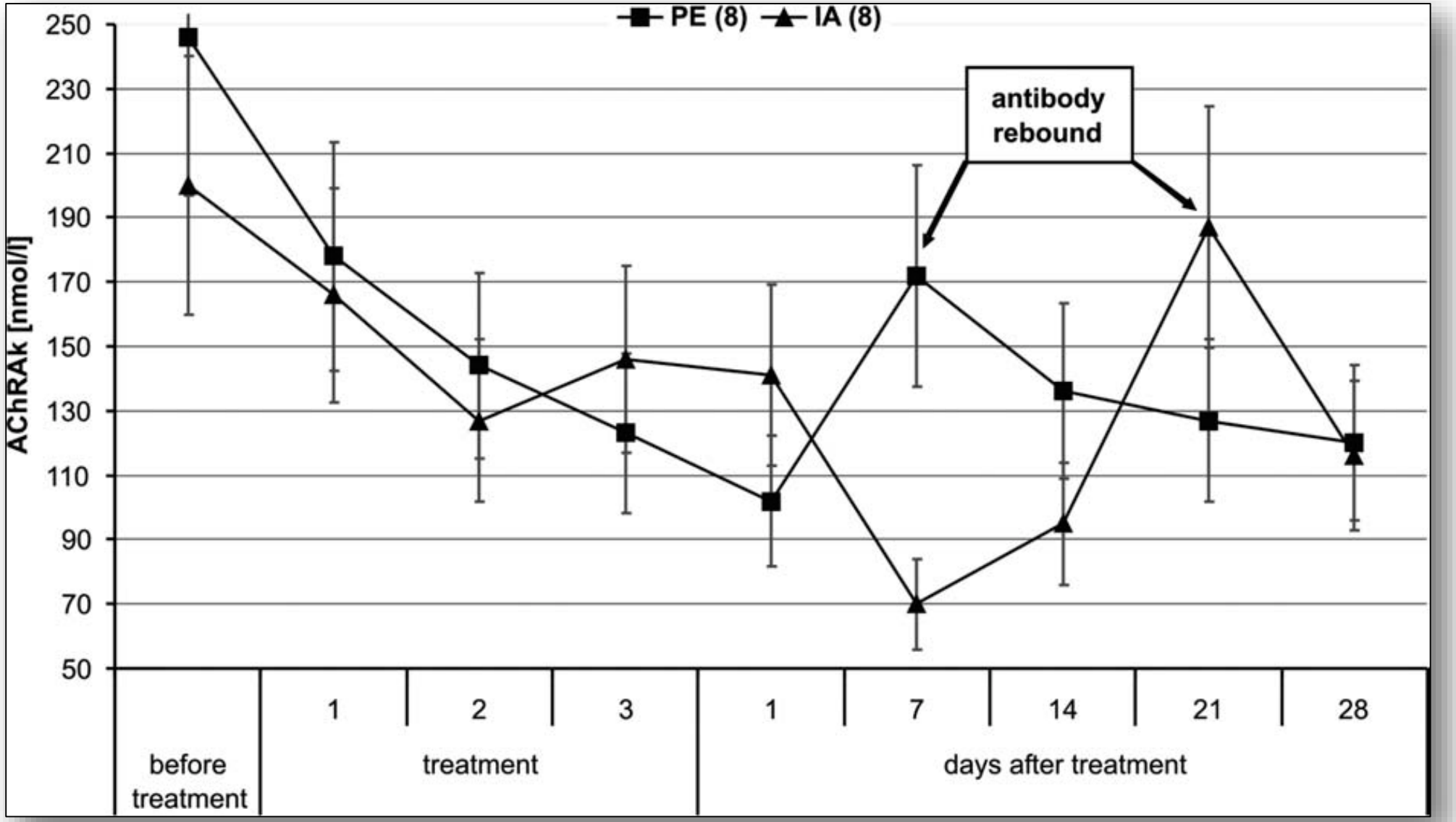
A Randomized and Controlled Study Comparing IA and Plasma Exchange in Myasthenic Crisis



KÖHLER et al.
Journal of Clinical Apheresis 26:347–355, 2011

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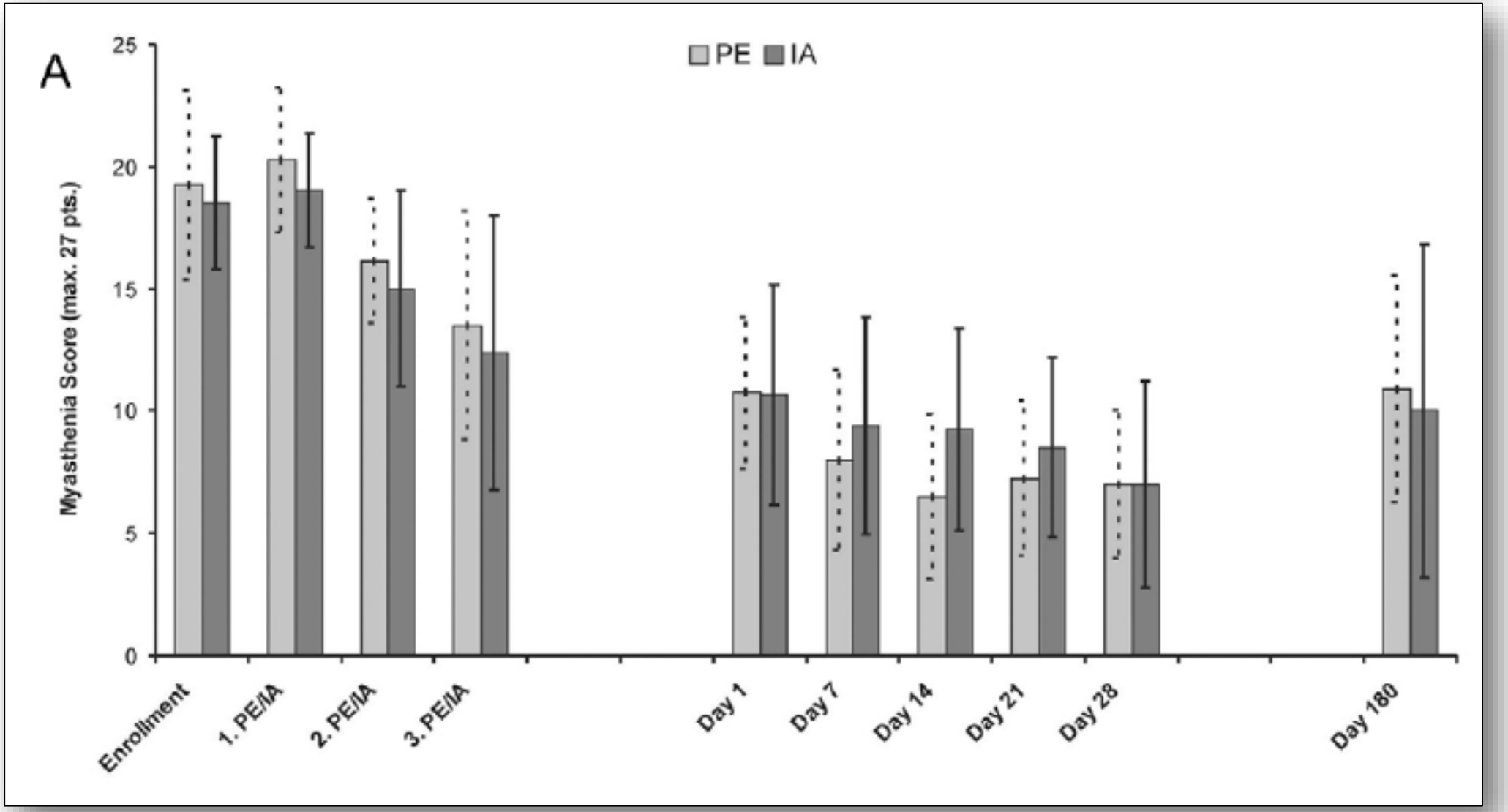

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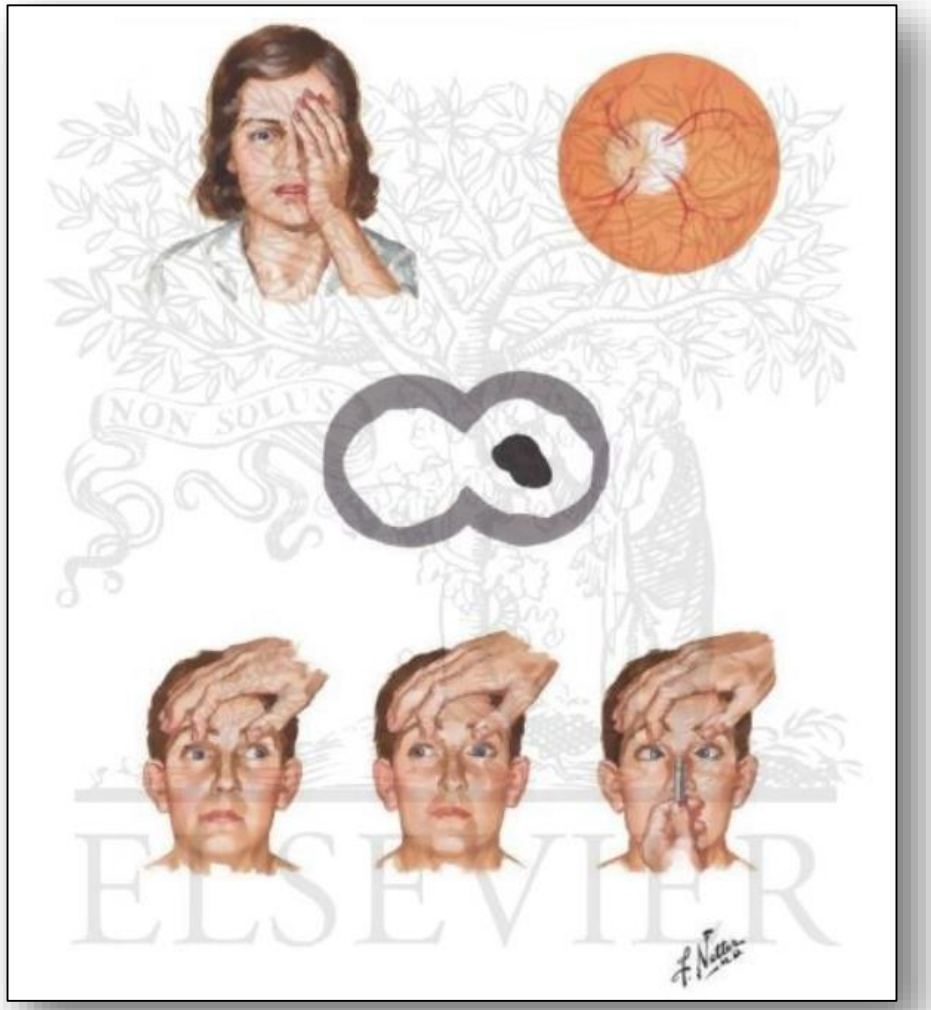
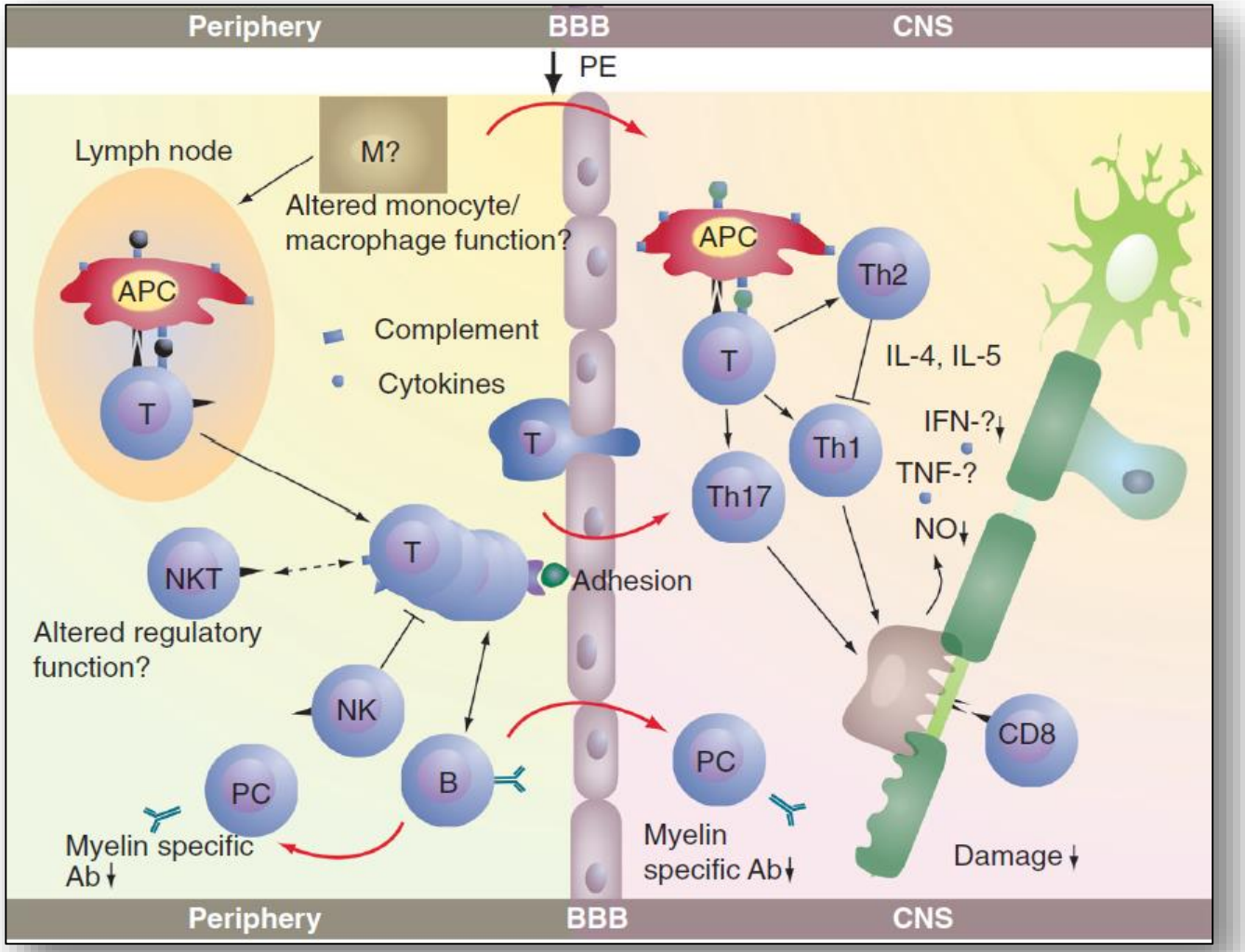
Multiple sclerosis





SCHRÖDER et al.
Expert Rev Neurother 9:1331-1339, 2009

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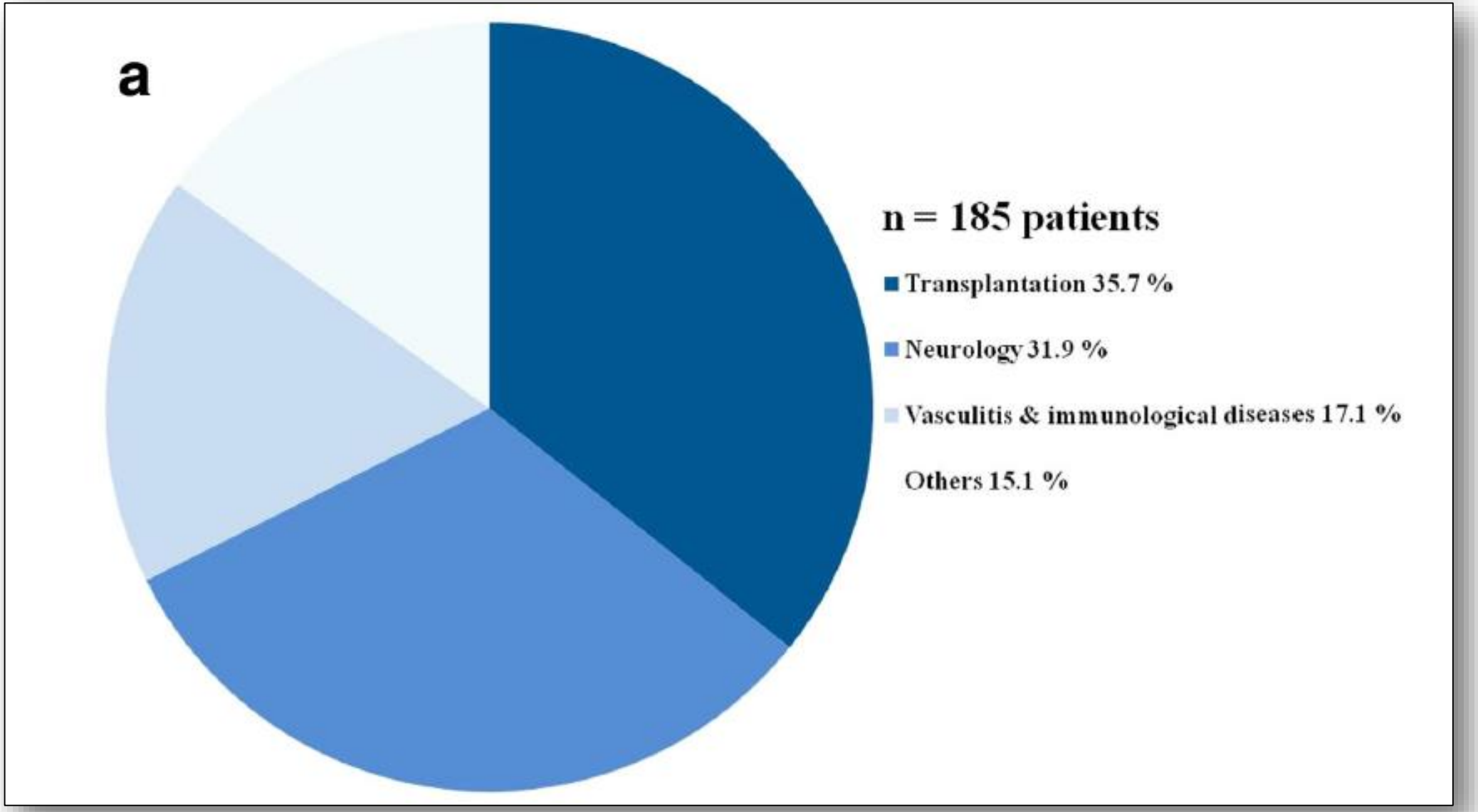
Therapeutic plasma exchange in a tertiary care center: 185 patients undergoing 912 treatments - a one-year retrospective analysis



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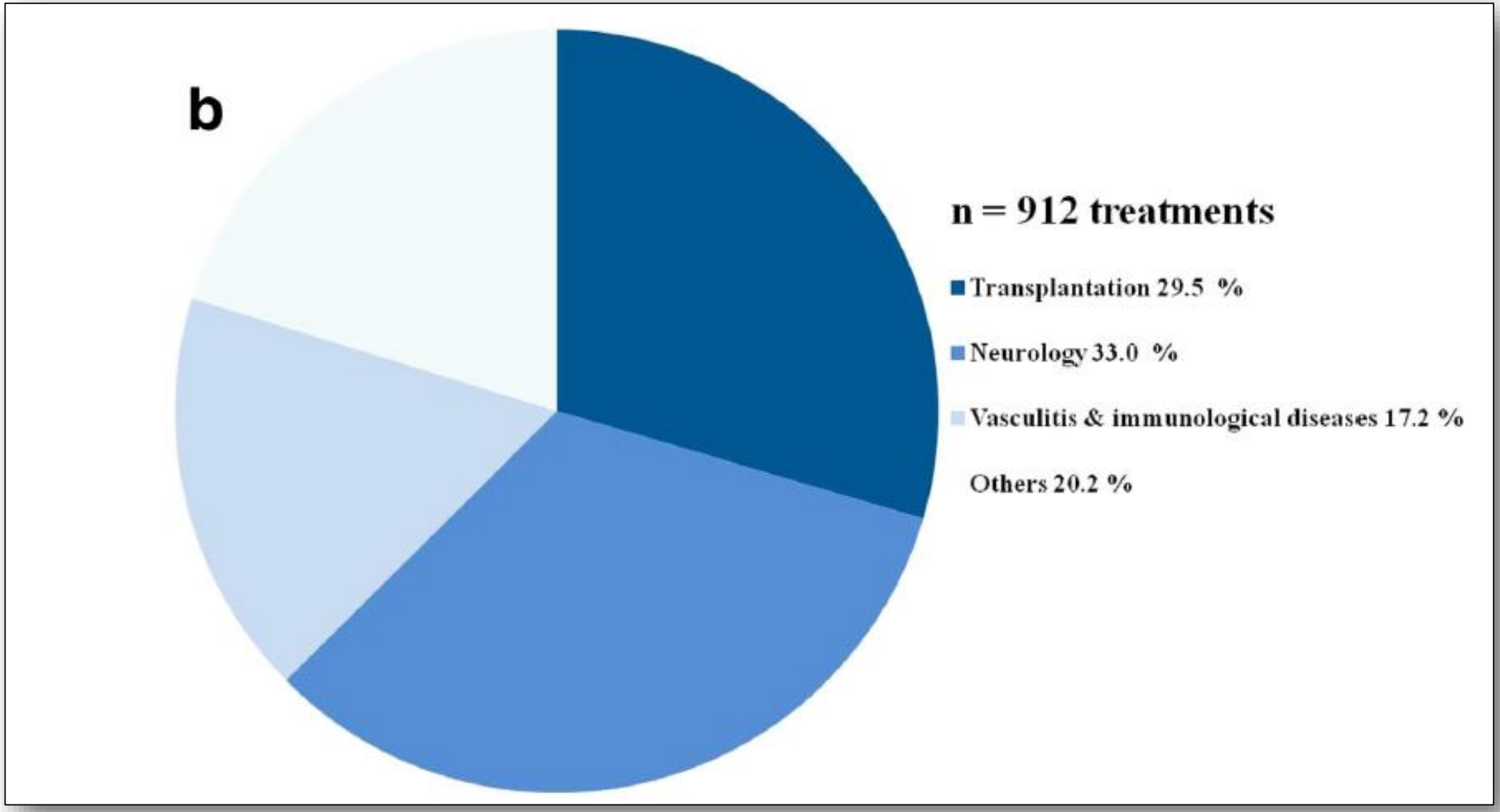

SCHMIDT et al.
BMC Nephrology 19:12, 2018

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Plasmapheresis in severe sepsis and septic shock: a prospective, randomised, controlled trial

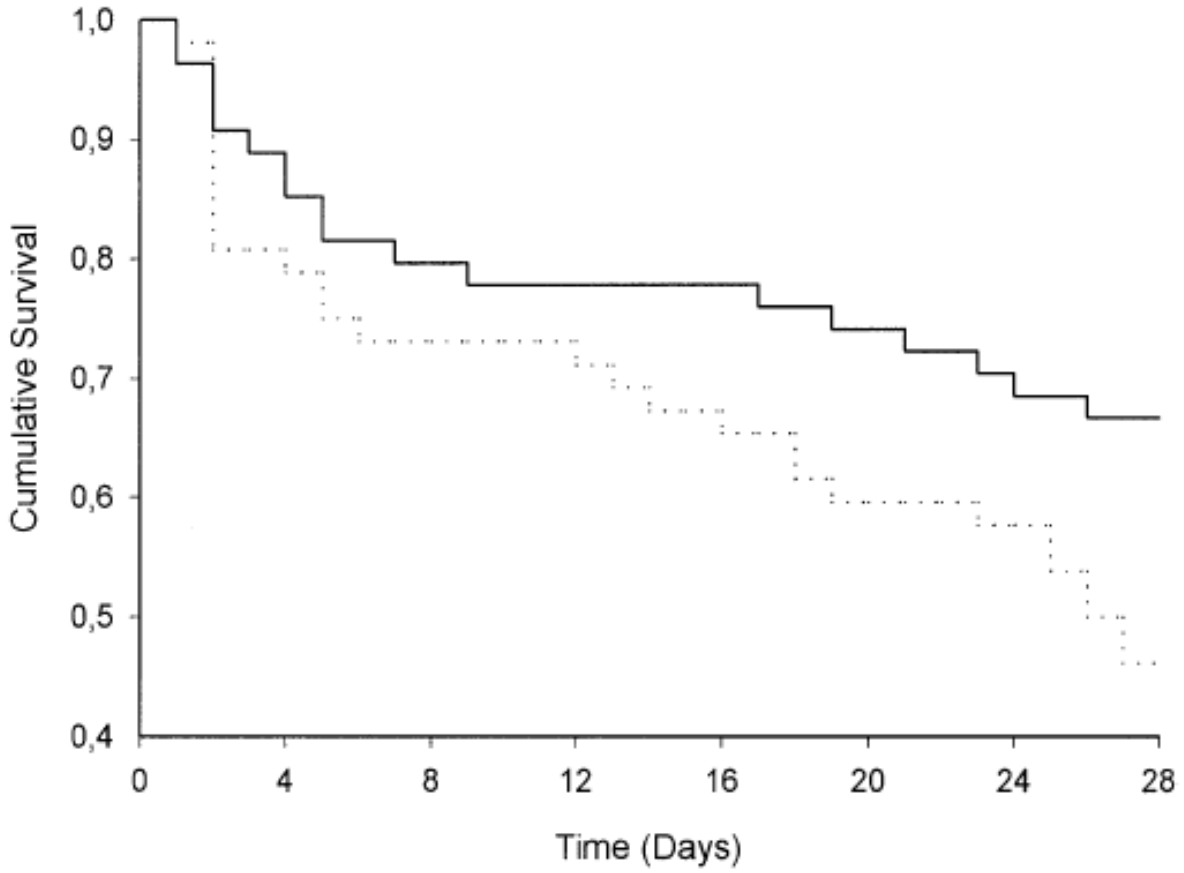

Fig. 1 Cumulative survival in 106 patients with severe sepsis or septic shock randomly assigned to plasmapheresis (*solid line*) or not (*dotted line*) in addition to standard sepsis treatment

BUSUND et al.
Intensive Care 28:1434–1439, 2002

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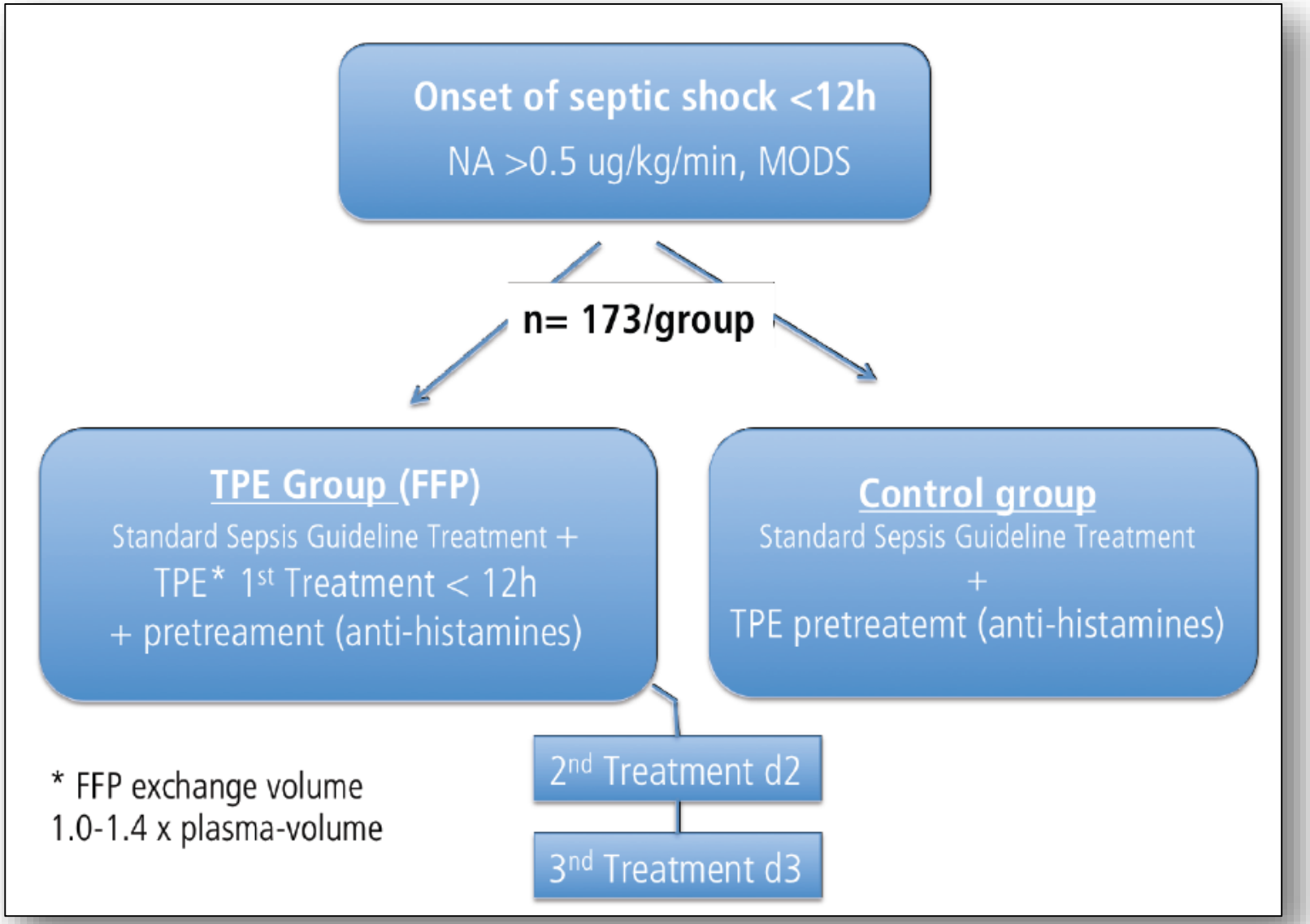
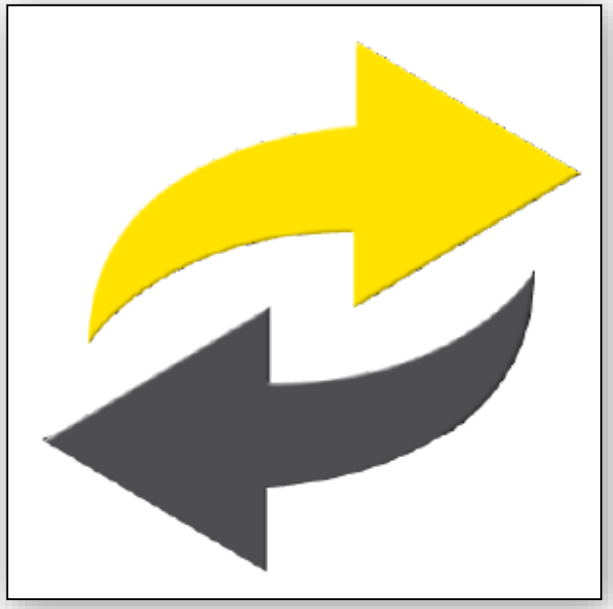
Randomized, prospective, multicenter, open-label, controlled, parallel-group trial investigating the efficacy of add-on plasma-exchange as an adjunctive strategy against septic shock with multiple organ dysfunction (EXCHANGE trial)





PI: PD Dr. Sascha David
Hannover Medical School, GERMANY

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Plasma exchange in severe pancreatitis´of a 36-year-old woman with BMI 45

Parameter	Ref	preTPE	post TPE
Lipase	8-78	**653**	**164**
Triglyceride	< 150	**2757**	**387**
Cholesterol	< 200	**716**	**177**
CRP	< 5	**303**	**179**

EDEN et al.
Med Klin IntensNotfmed. 112(5):471-474, 2017

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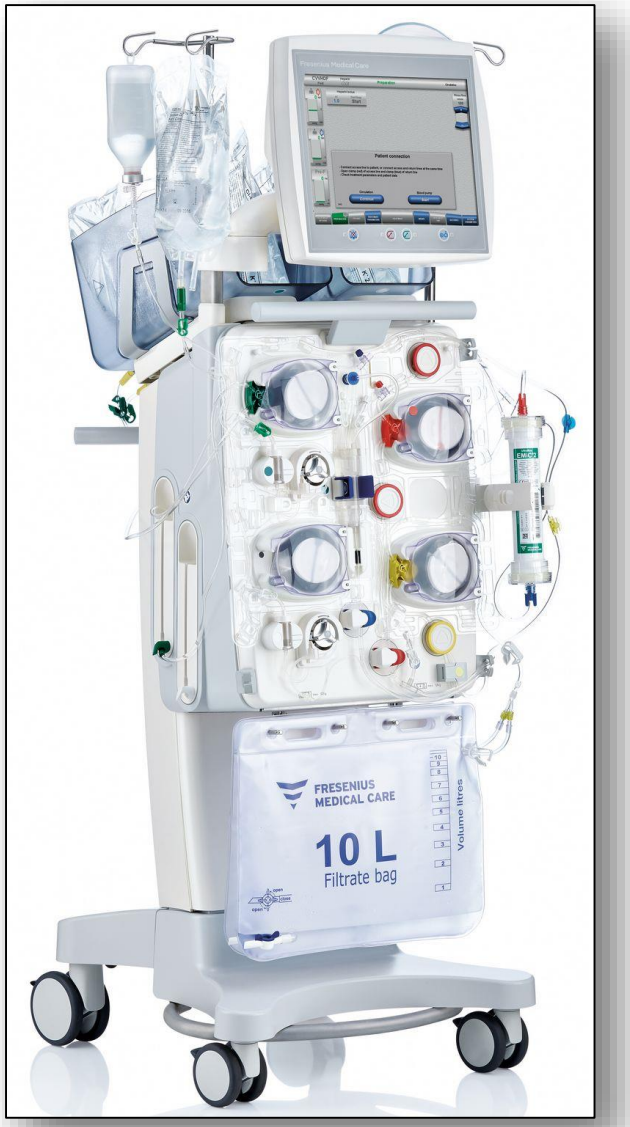
mTPE



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cTPE

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Membrane vs centrifuge-based TPE: a randomized prospective crossover study

- Patients: Age: 51.6 ± 13.5

  Female 10 (47.6%)

  BMI (kg/m²) 25.1 ± 5.0

- randomized to either membrane or centrifuge for 1st treatment
- 2nd treatment performed in an cross-over design

HAFER et al.
Int Urol Nephrol 55-015-1137-3, 2015

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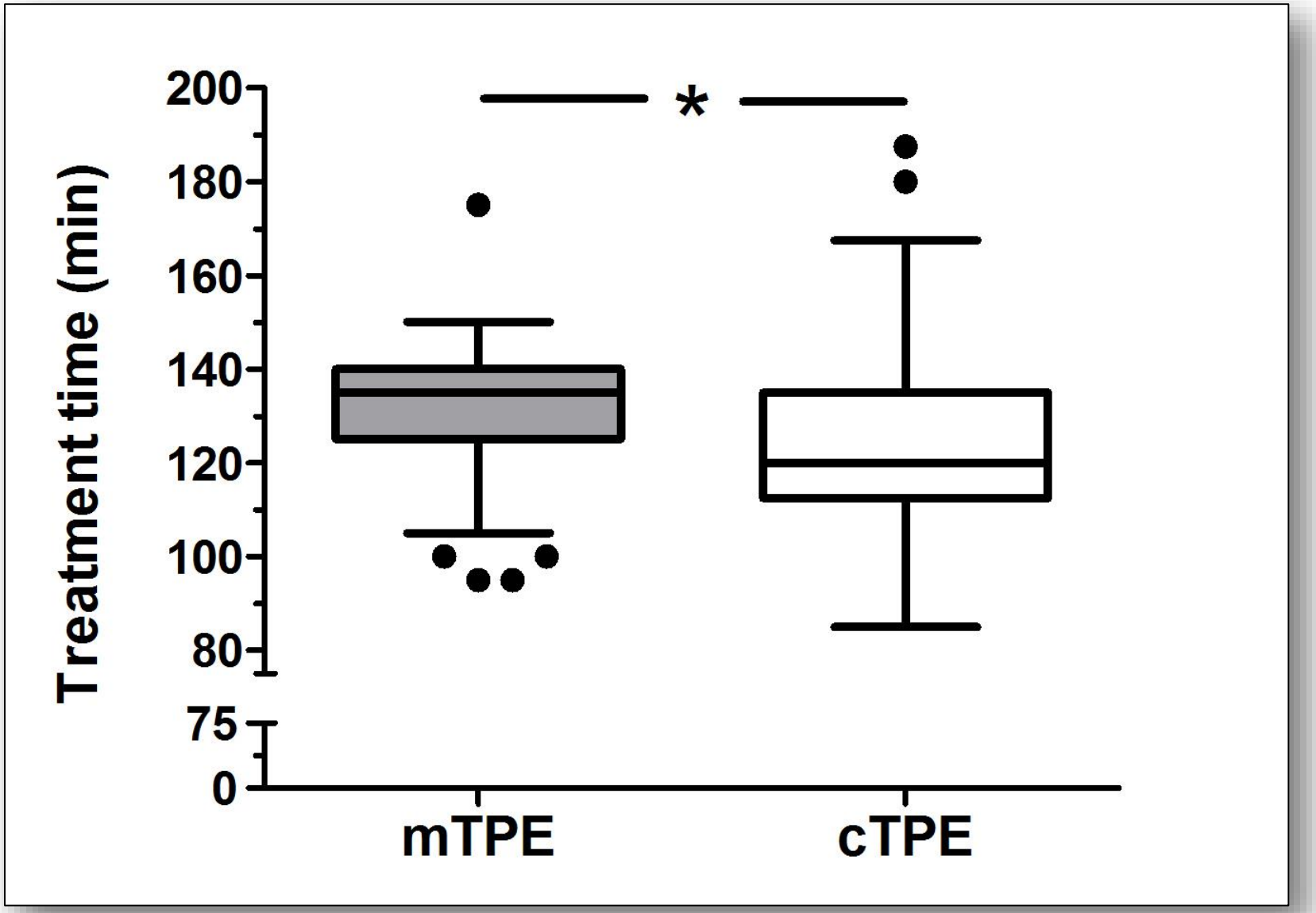

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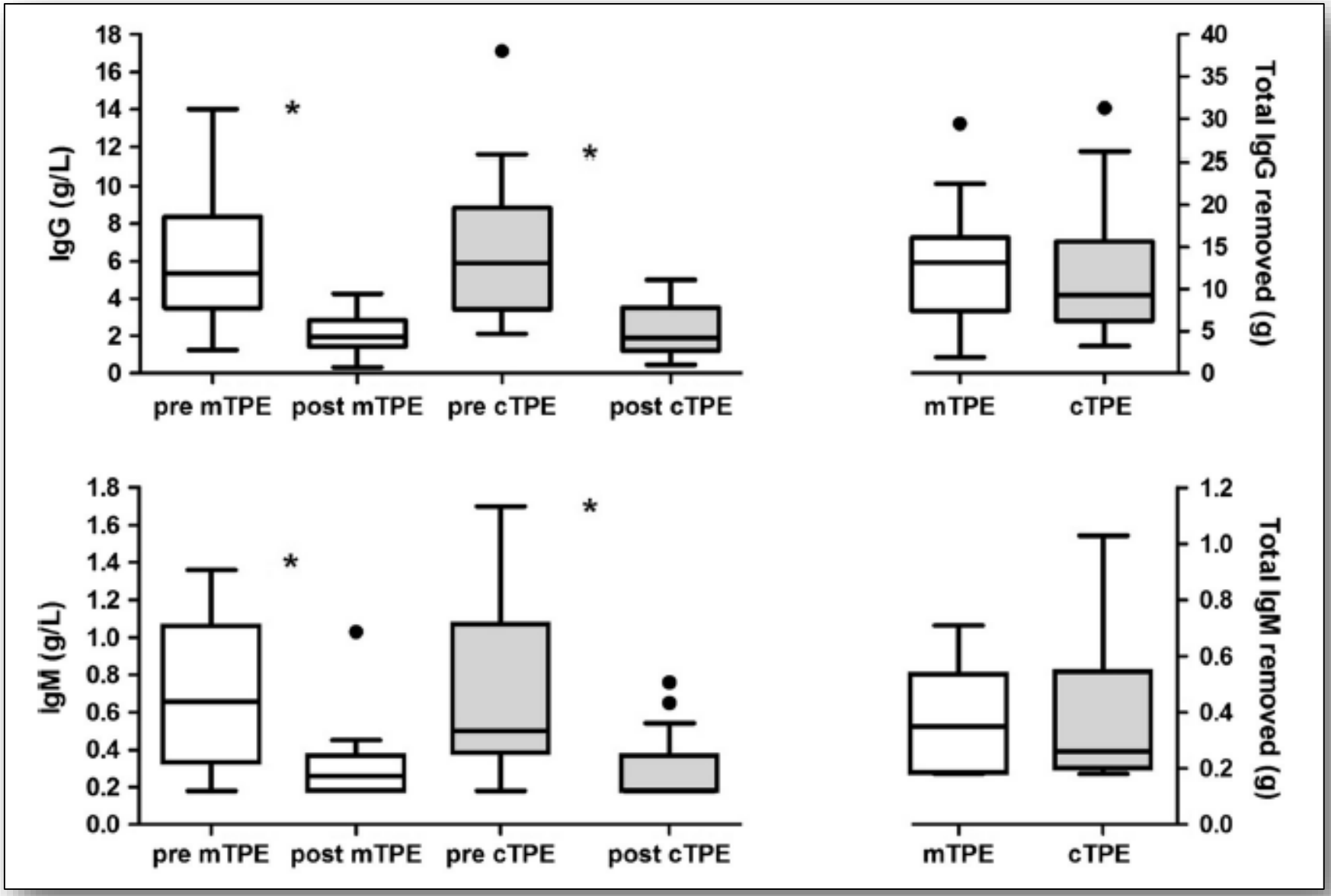

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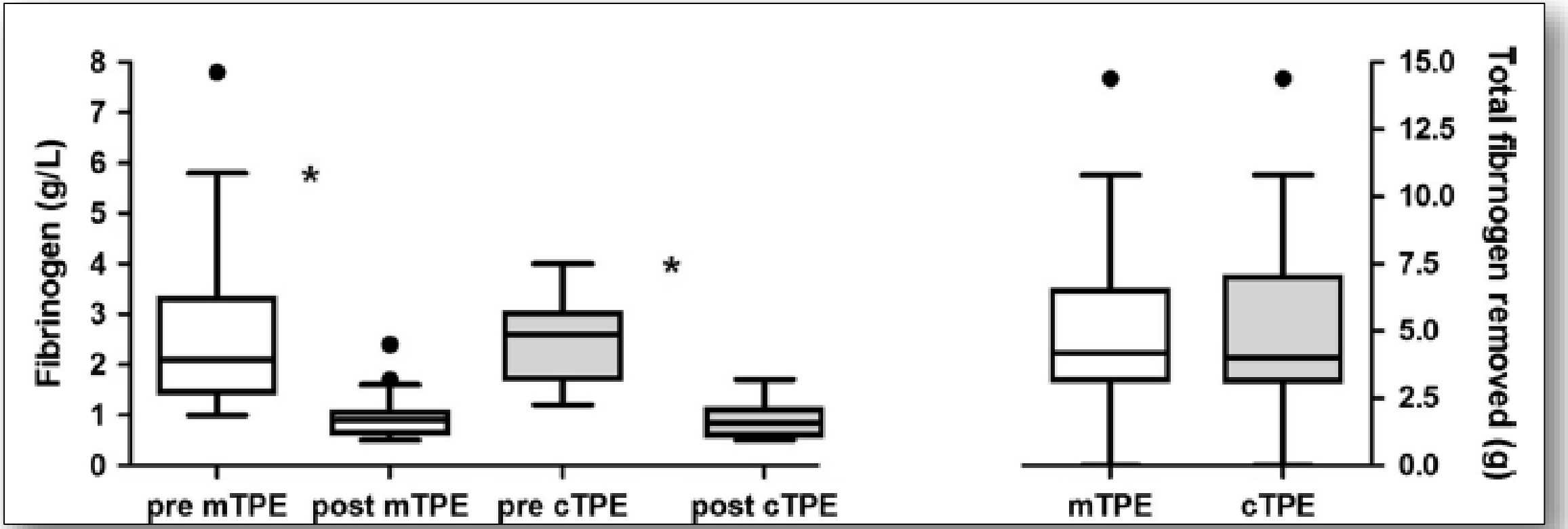

HAFER et al.
Int Urol Nephrol 55-015-1137-3, 2015

Membrane vs centrifuge-based TPE: a randomized prospective crossover study

- **mTPE** treatment (**heparin**) **TMP**
  - start of treatment 14.0 [9.0-19.5] mm Hg
  - end of treatment 21.0 [13.5-26.0] mmHg (p=0.048)
- **cTPE** treatment (**citrate**) **ionized Ca++**
  - start of treatment 1.17 [1.13 – 1.21]
  - end of treatment 1.13 [1.08 – 1.18] mmol/l (p=0.13)

HAFER et al.
Int Urol Nephrol 55-015-1137-3, 2015

Membrane vs centrifuge-based TPE: a randomized prospective crossover study

Parameter	unit	mTPE before	mTPE after	cTPE before	cTPE after
Hematocrit	%	33.90 (31.08 – 37.80)	32.79 (28.83 – 37.65)	33.85 (30.33 – 37.98)	34.95* (30.93 – 38.43)
Hemoglobin	g/dl	11.30 (10.03 – 11.98)	10.90 (9.45 – 12.15)	11.10 (10.03 – 12.23)	11.50* (10.23-12.28)
PLT	Mill/L	237.5 (176.3-310.0)	209.5* (141.5-254.5)	235.5 (174.0-284.8)	222.0* (151.0-293.0)
Leukocytes	$10^3/\mu L$	8.00 (3.92 – 11.43)	8.55* (5.47-13.3)	6.70 (4.82-13.03)	7.30* (5.37 – 13.95)

HAFER et al.
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HAFER et al.
Int Urol Nephrol 55-015-1137-3, 2015

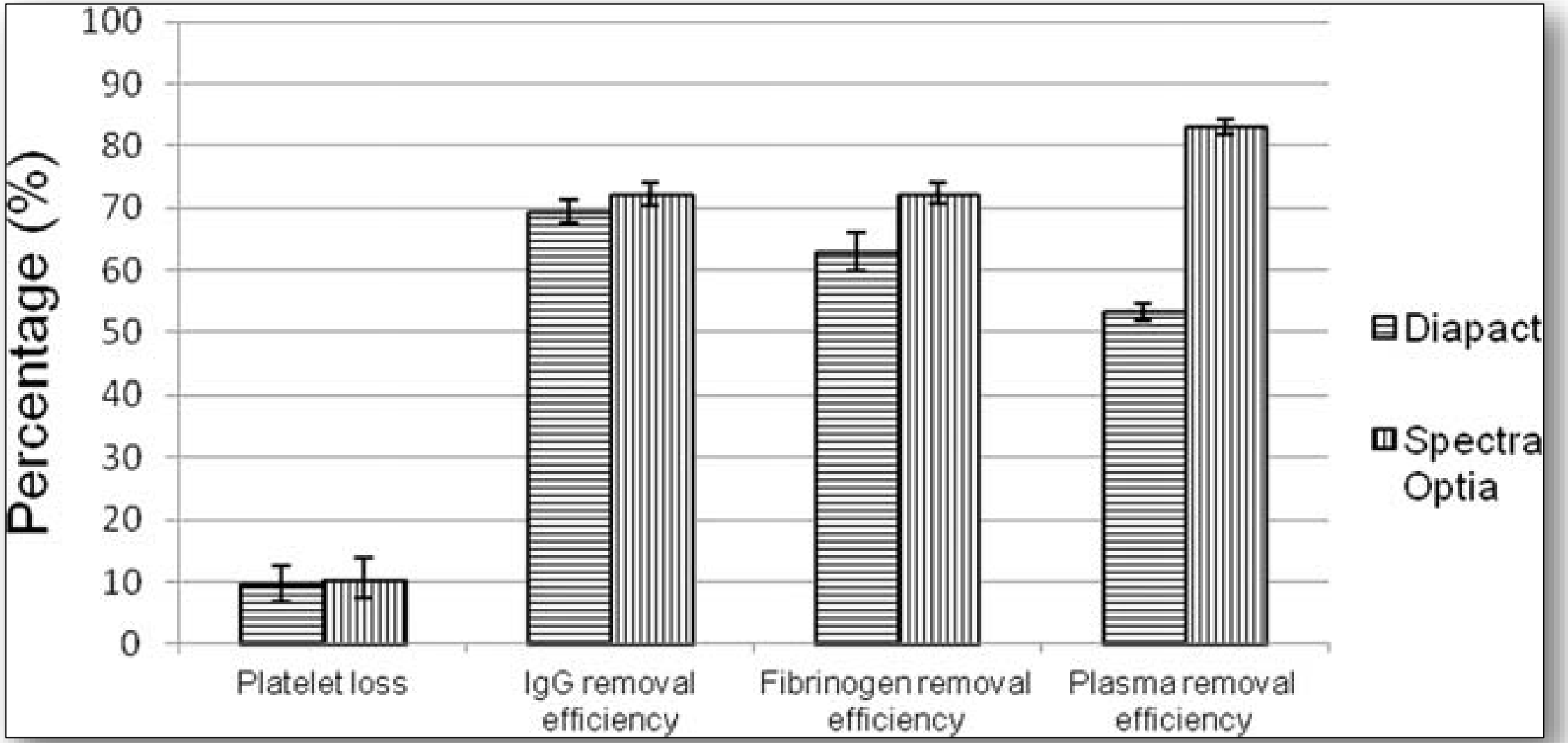
A randomized crossover study comparing mTPE cTPE procedures

TABLE 2. Summarizing table of several comparative variables analyzed on 27 patients in this study*

Variable	Diapact	Spectra Optia
TBV (L)	4,574 ± 793	
Total plasma volume (L)	2,945 ± 515	2,976 ± 554
Setup time (min)†	7 ± 1	5 ± 1
Priming time (min)†	16 ± 1	6 ± 1
Preparation time (min)†	23 ± 2	11 ± 1
Procedure time (min)†	134 ± 26	91 ± 25
Total time (min)†	157 ± 26	102 ± 25
Time to remove 1 L of plasma (L/min)†	36.9 ± 5.5	24.5 ± 6.5
Mean flow rate (mL/min)	82.4 ± 11.8	80.6 ± 11.8
Removed plasma volume (mL)‡	3,676 ± 635	3,745 ± 641
Replacement fluid used (mL)§	3,624 ± 658	3,722 ± 635

KES et al.
Transfusion. 56(12):3065-3072, 2016

A randomized crossover study comparing mTPE cTPE procedures



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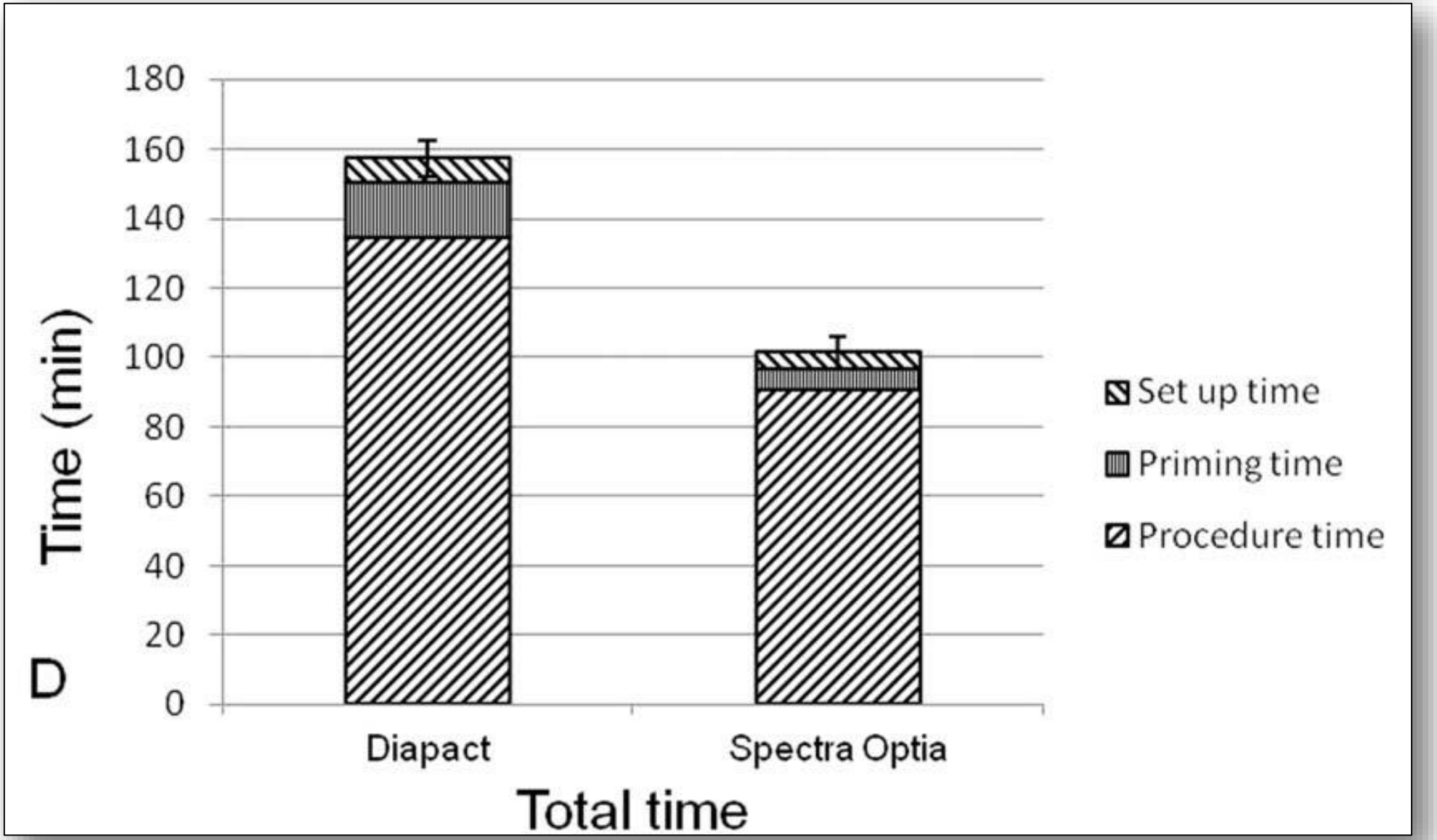

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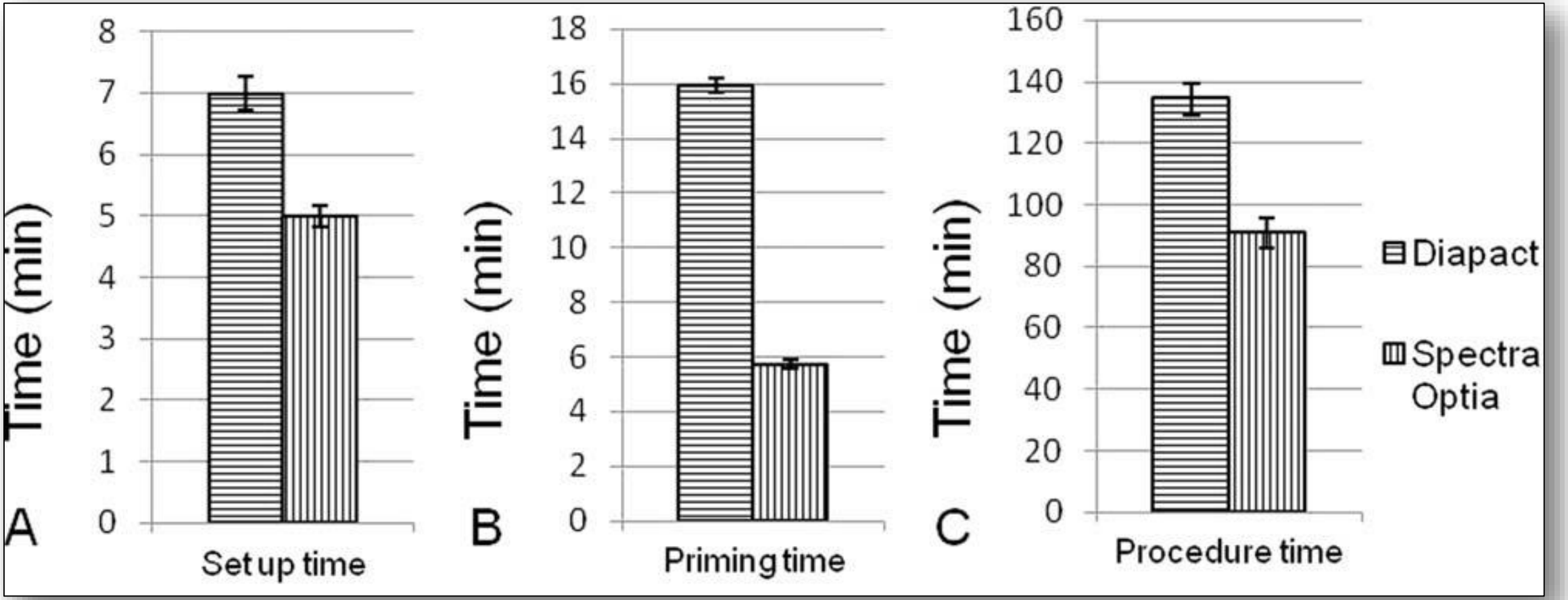

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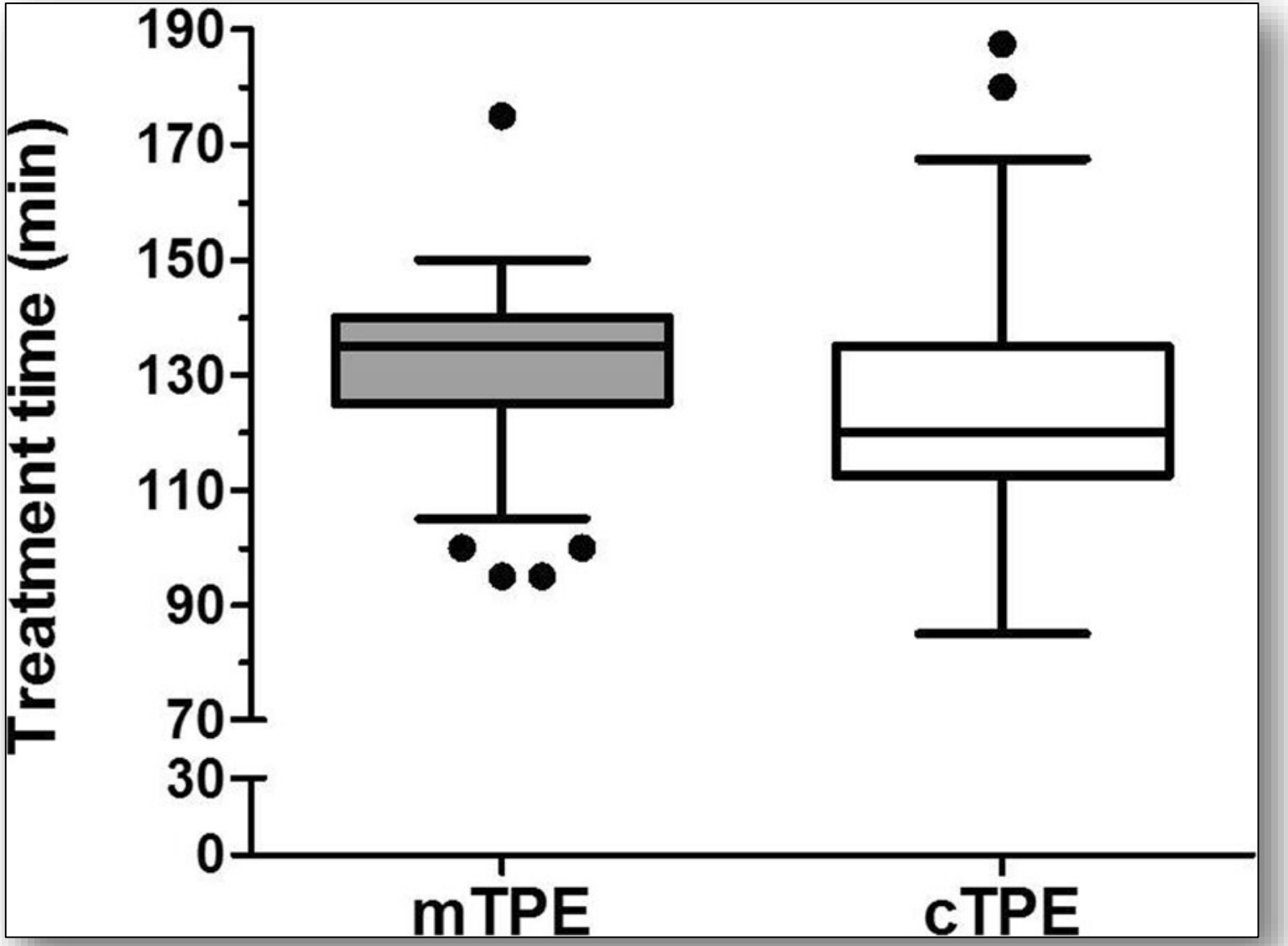
Klinikum Braunschweig

Therapeutic plasma exchange in a tertiary care center: 185 patients undergoing 912 treatments - a one-year retrospective analysis



SCHMIDT et al.
BMC Nephrology 19:12, 2018

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cTPE or mTPE		
	membrane	centrifuge
preparation time	(+)	+
access | blood flow	(+)	+
single needle	-	+
efficacy	(+)	+
add on procedures	+	+
time per treatment	-	+
swiss army knife	+	-

cTPE or mTPE

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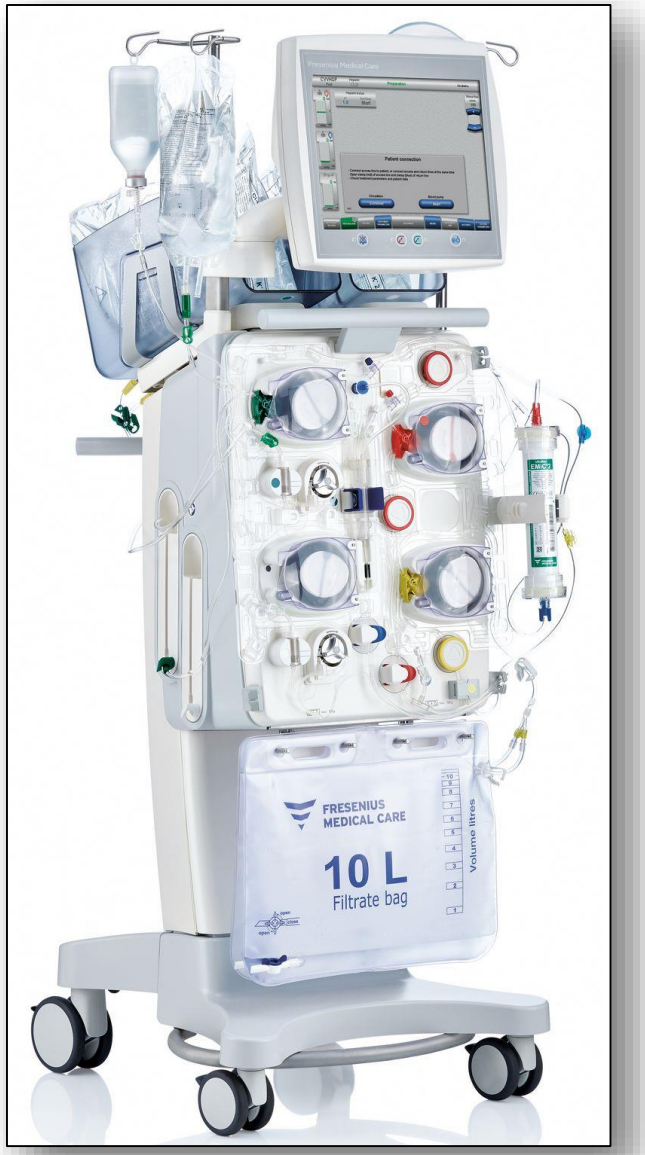
Versatility



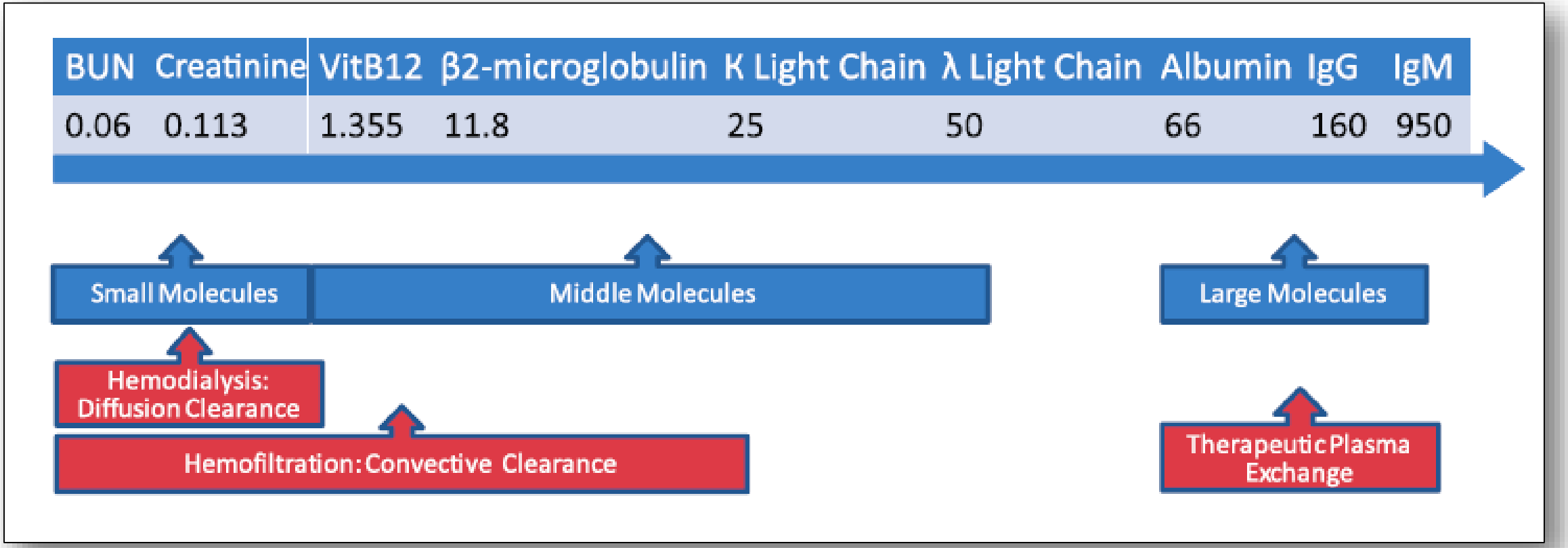
Principles of separation: indications and therapeutic targets for plasma exchange

Table 2. Operational contrasts between centrifuge and membrane apheresis procedures

Characteristic	Centrifuge Therapeutic Plasma Exchange	Membrane Therapeutic Plasma Exchange
Mechanism	Centrifugal force	Capillary membrane filter
Blood flow (ml/min)	10–150	150
Plasma extraction (%)	80	30
Plasma removal (ml/min)	Variable	30
Anticoagulation	Citrate	Heparin
Separation	Specific gravity	Size
Blood volume in circuit (ml)	Approximately 180	125
Molecular weight cutoff (D)	N/A	3 million
Sterilization	γ Irradiation or ethylene oxide	Ethylene oxide
Fluid replacement	Albumin, fresh frozen plasma	Albumin, fresh frozen plasma

WILLIAMS & BALLOGUN
Clin J Am Soc Nephrol 9(1):181-90, 2014

Principles of separation: indications and therapeutic targets for plasma exchange



WILLIAMS & BALLOGUN
Clin J Am Soc Nephrol 9(1):181-90, 2014

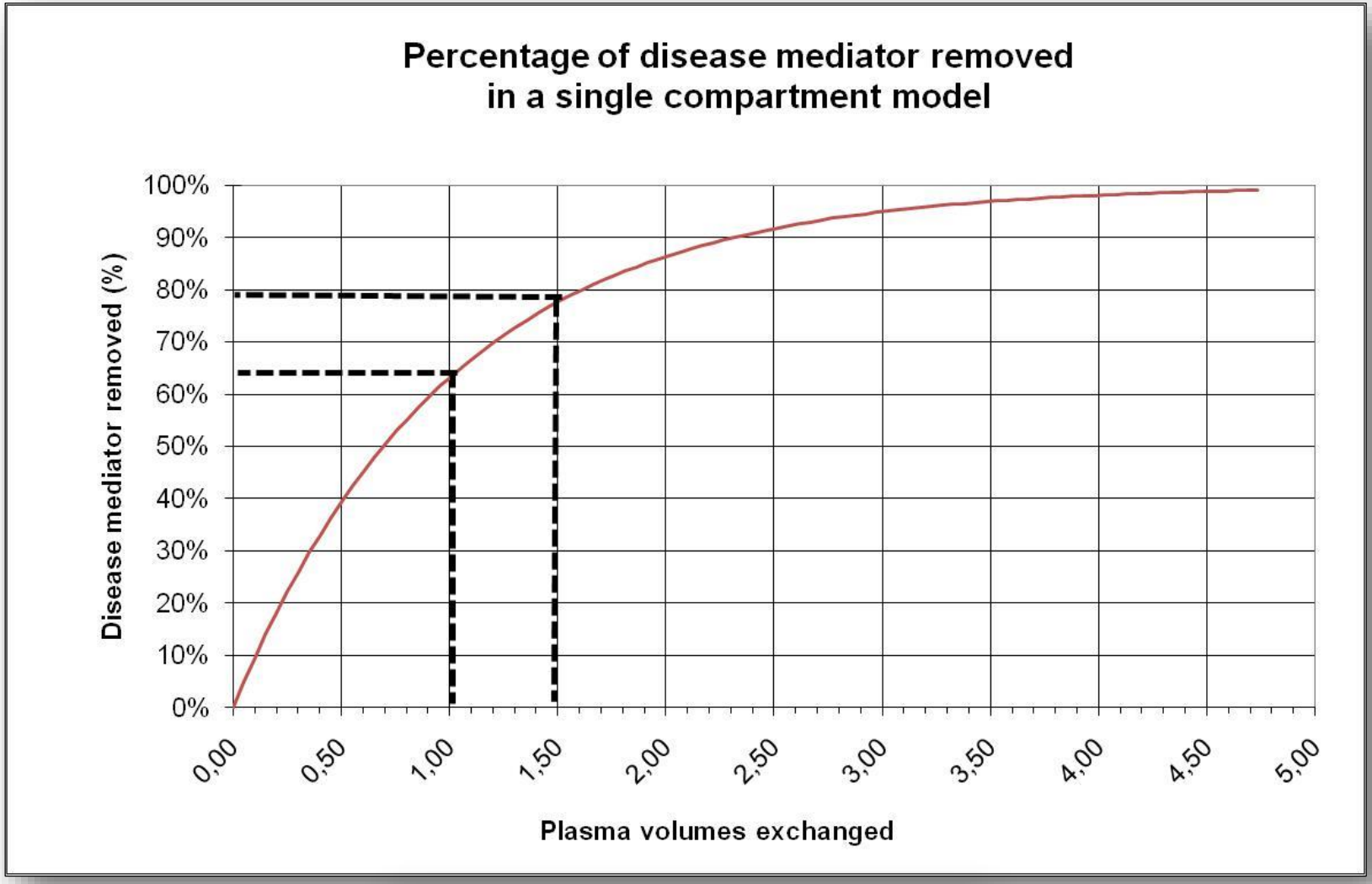
Therapeutic Plasmaexchange
few answers and many question

1) Who should be treated?

2) Which device should we use?

3) How to define treatment dose?

A simple and accurate method for prescribing plasma exchange



EPV = [0.065 X wt(kg)] X [1-Hct]

KAPLAN
ASAIO Trans 36: M597-M599, 1990

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Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group

Study Design

Patients were randomly assigned to receive either plasma exchange or plasma infusion with fresh-frozen plasma, according to a scheme that ensured a balanced allocation within each center. One group received plasma exchange with fresh-frozen plasma as the replacement for a minimum of seven procedures over the first nine hospital days, with treatment on the first three days being essential. The volume exchanged was 1.5 times the predicted plasma volume for the first three procedures, and 1.0 times the predicted volume thereafter. The other group received plasma infusion daily until the

ROCK et al
N Engl J Med. 325(6):393-7, 1991

Klinikum Braunschweig

Assessment of Hemostasis after Plasma Exchange Using Rotational Thrombelastometry (ROTEM)

Therapeutic plasma exchange (TPE)

According to the standard protocol of our center, prior to first TPE, a central venous dialysis catheter was inserted into the internal jugular vein. TPE was performed using a COM.TEC cell separator (Fresenius Hemo-Care GmbH, Bad Homburg, Germany). All patients were treated five times with 2L albumin 5% (0.4 to 1.0 plasma volumes) per session using an interval of 1–2

"All patients were treated five times with 2L albumin 5% (0.4 to 1.0 plasma volumes) per session…."

THÖLKING et al. PLoS ONE 10(6): e0130402, 2015

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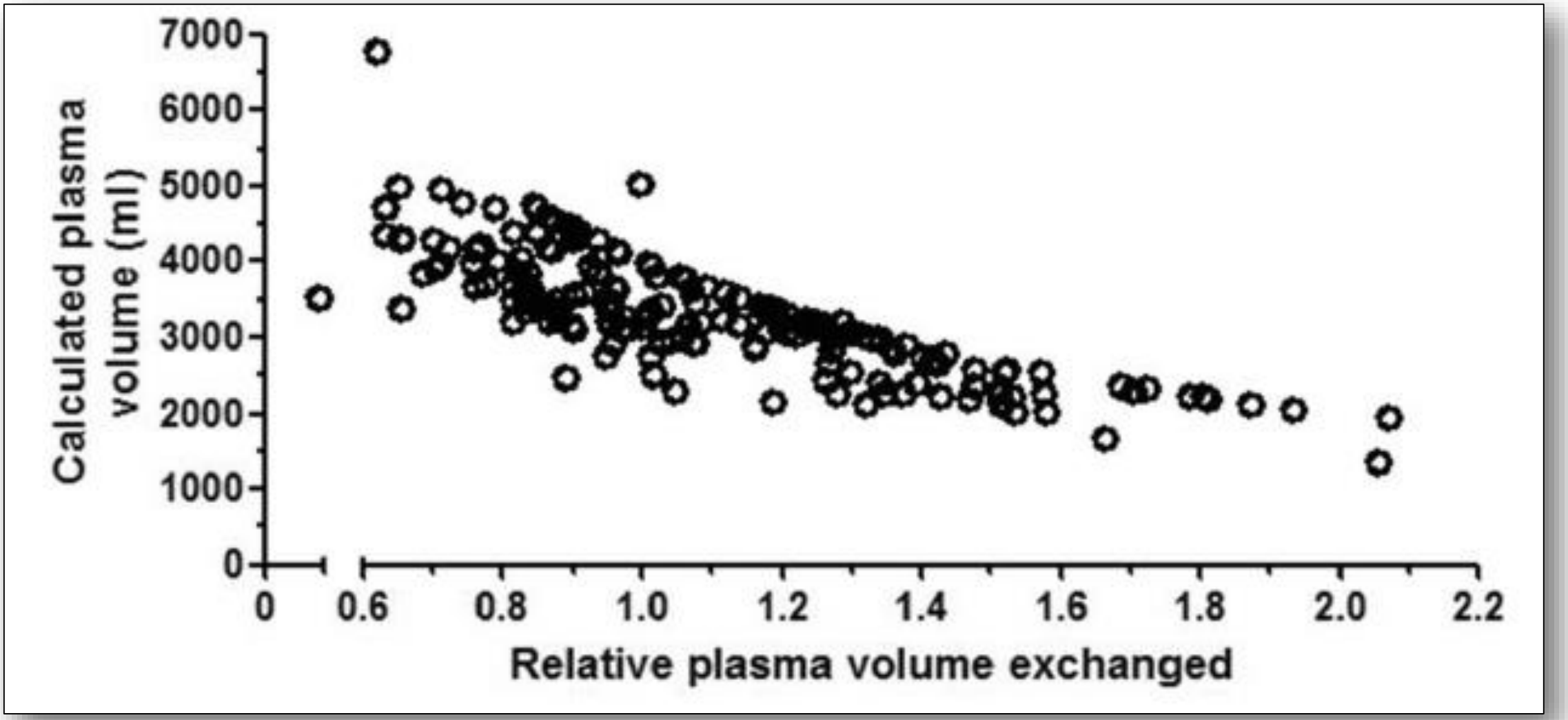
Therapeutic plasma exchange in a tertiary care center: 185 patients undergoing 912 treatments - a one-year retrospective analysis



SCHMIDT et al.
BMC Nephrology 19:12, 2018

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Therapeutic plasma exchange in a tertiary care center: 185 patients undergoing 912 treatments - a one-year retrospective analysis

	All ($n = 185$)	Neurology ($n = 59$)	Transplantation ($n = 66$)	Vasculitis and Immunological Disease ($n = 32$)	Others ($n = 28$)	One way ANOVA P value
Age (years)	54.0 [43.0–64.0]	56.0 [39.0–67.0]	54.0 [47.0–62.0]	54.5 [47.3–64.5]	51.5 [32.5–63.8]	0.2738
Sex (m/f)	95/90	29/30	35/31	16/16	15/13	NS
BMI (kg/m^2)	25.5 [22.4–29.3]	24.8 [21.7–28.2]	24.3 [22.3–27.8]	26.1 [22.6–30.6]	24.7 [22.0–28.4]	0.1416
Hct (%)	33.9 [29.8–39.2]	40.2 [37.5–42.9]	33.7 [31.0–37.0]	30.5 [27.0–33.6]	24.6 [20.2–31.2]	< 0.0001
PV_{calc} (ml)	3240 [2737–3849]	3058 [2533–3359]	3194 [2545–3658]	3984 [3433–4439]	3699.5 [3125–4149]	< 0.0001
PV_{calc} NADLER (ml)	3131 [2708–3594]	2846 [2542–3182]	3083 [2543–3571]	3501 [3199–3972]	3631 [3123–3916]	< 0.0001
PV_{ex} (ml)	3500 [3028–3987]	3599 [3101–4000]	3600 [3165–4000]	3443 [3037–3893]	2998 [2823–3576]	< 0.0001
PV_{ex}/PV_{calc}	1.01 [0.86–1.28]	1.17 [0.97–1.38]	1.16 [0.94–1.34]	0.88 [0.79–0.99]	0.83 [0.70–0.96]	< 0.0001
$PV_{40ml/kg}$	3080 [2600–3560]	3080 [2580–3420]	2950 [2465–3285]	3540 [3140–3990]	3174 [2630–3480]	0.0004
$PV_{calc}/PV_{40ml/kg}$ (%)	+ 4.94%	- 0.72%	+ 7.64	+ 11.2%	+ 14.21%	p <0.0001
$PV_{ex}/PV_{40ml/kg}$ (%)	+ 12.00%	+ 14.42%	+ 18.06%	- 2.82%	- 5.91%	p <0.0001
Treatments (n)	5 [3–5]	5 [5–5]	4 [3–5]	5 [3–7]	4 [2–8]	0.0078
1st - 5th TPE (d) ($n = 61$)	7 [6–10]	7.5 [7–10]	7 [6–11]	6.5 [6–7.75]	4 [4–5.5]	p <0.0001
Exchange fluid (%)						
Albumin	54.1	88.4	56.2	37.6	9.2	p <0.0001
FFP	34.7	7.6	22.1	45.2	87.0	p <0.0001
Mix	11.2	4.0	21.7	17.2	2.7	p <0-0001

SCHMIDT et al.
BMC Nephrology 19:12, 2018

Pro: High dose of therapeutic plasma exchange-mind the gap!

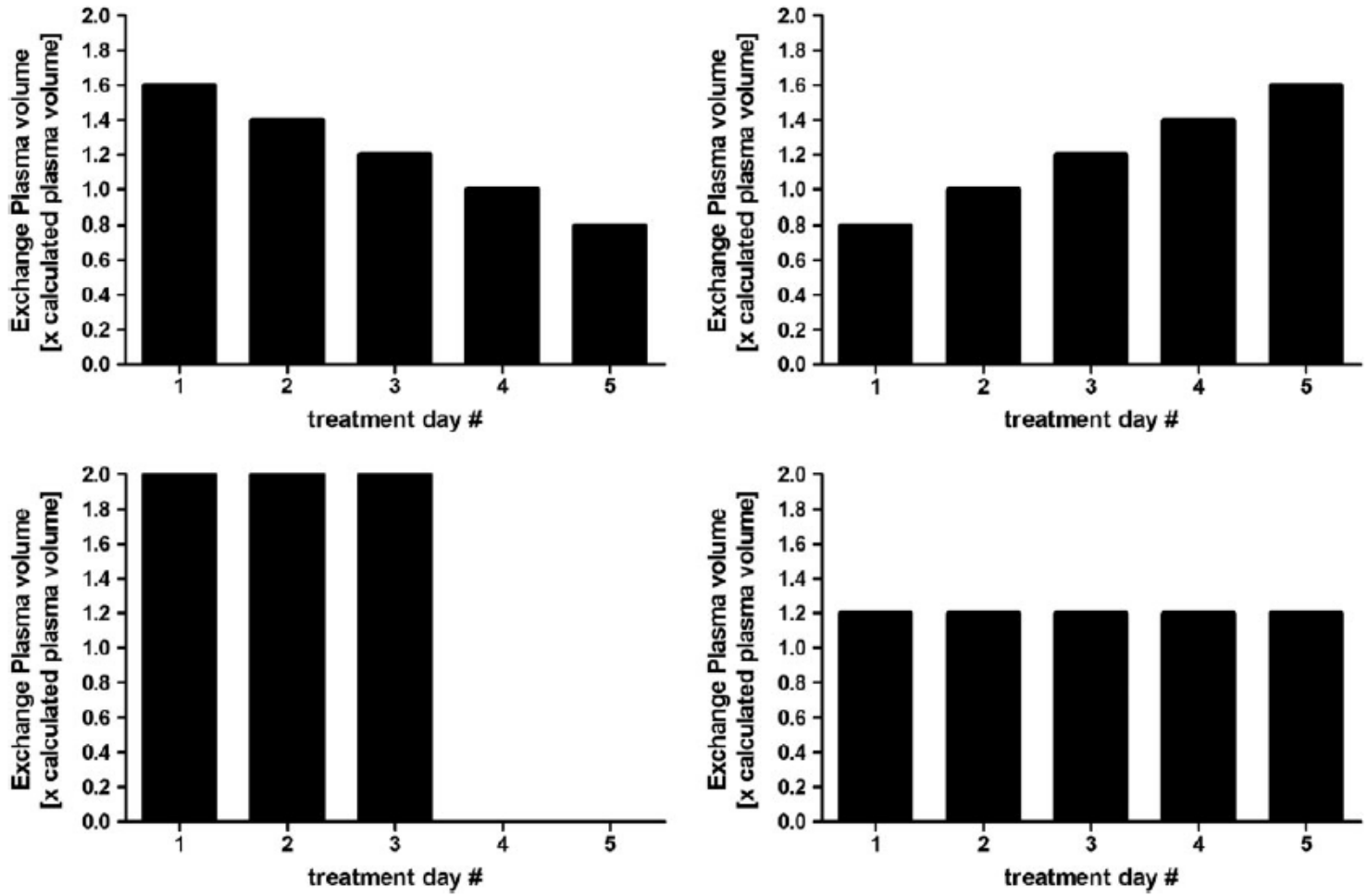
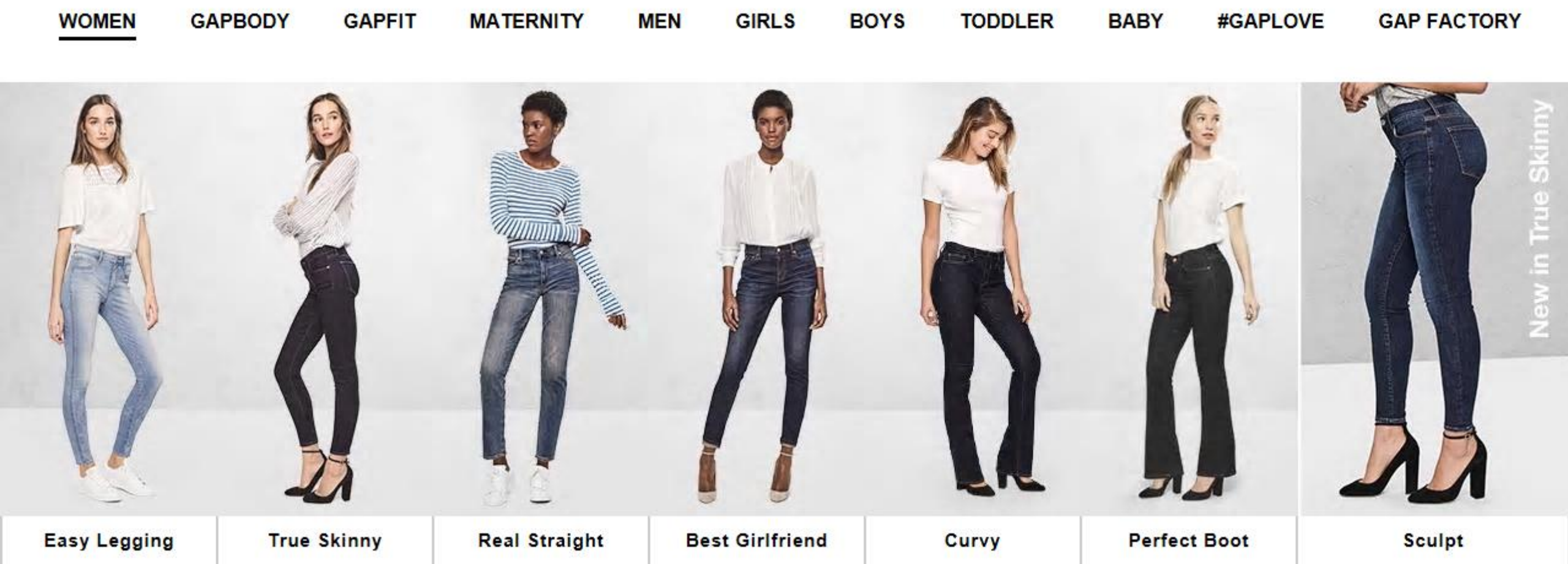


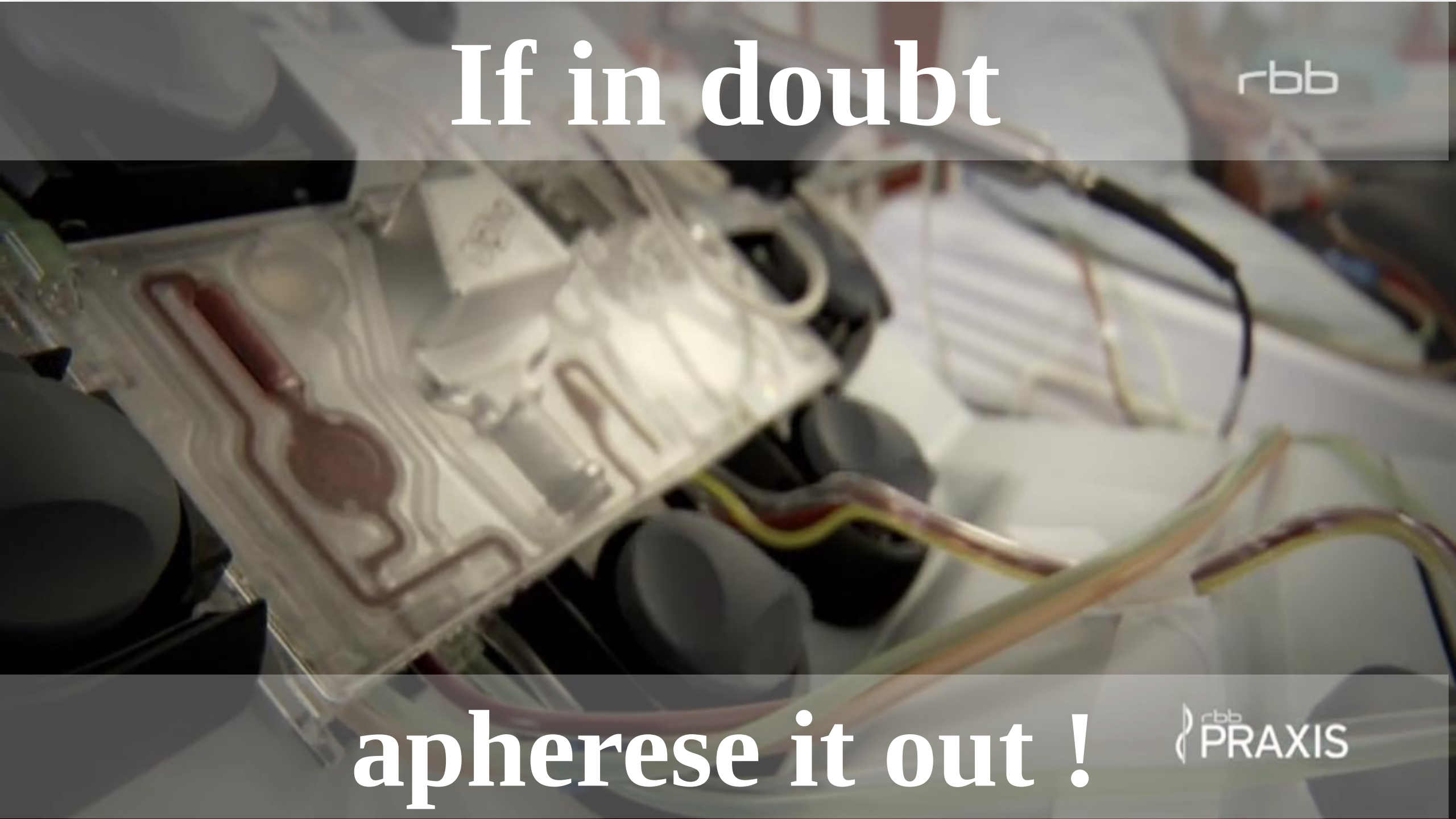
FIGURE 1: Time-averaged plasma exchange volume of 6 times TPV delivered in four different ways: decremental TPE (TTP), incremental TPE (desensitization), high-volume TPE (sepsis, liver failure) and equal dose TPE (GBS).

Nephrol Dial Transplant. 1;32(9):1457-1460

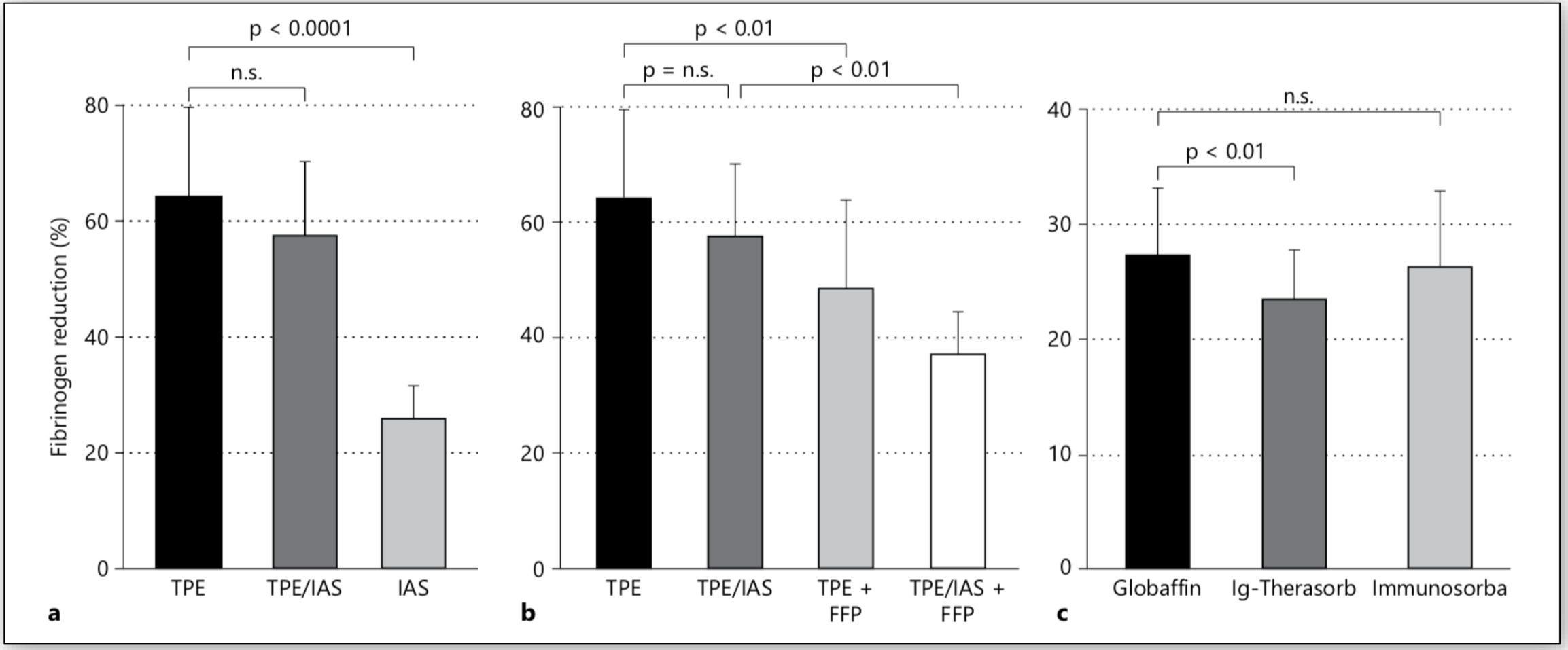
HAFER & KIELSTEIN

Let`s close the GAP




If in doubt
rbb
apherese it out !
rbb PRAXIS

Fibrinogen Reduction and Bleeding Complications in Plasma Exchange, Immunoadsorption and a Combination of the Two



ZÖLLNER et al.
Blood Purif 38:160–166, 2014

Klinikum Braunschweig