



ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΑΙΜΑΦΑΙΡΕΣΗΣ

# Ανασκόπηση στις τεχνικές των μεθόδων Αφαίρεσης - Διπλή Διήθηση

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## Ορισμός

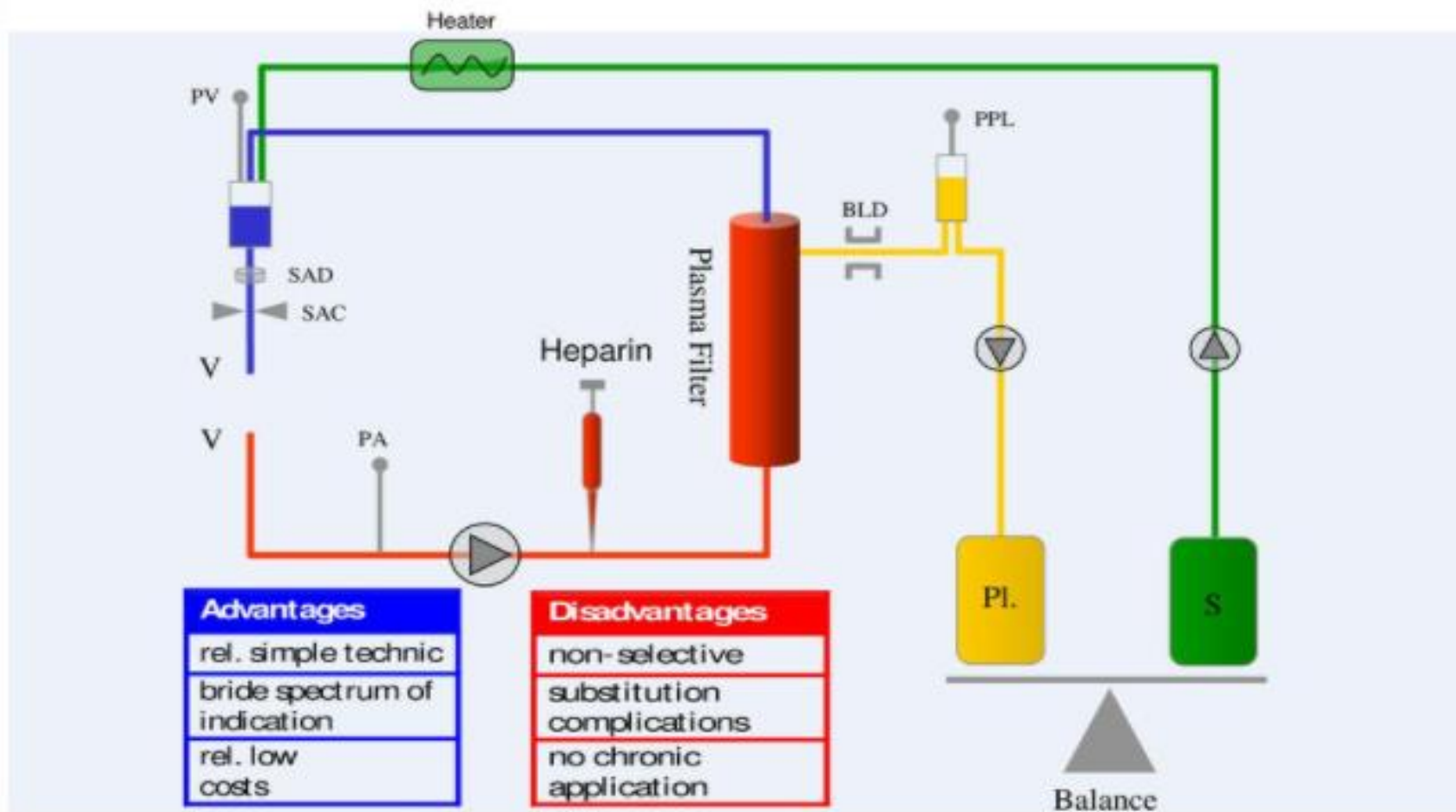
**Therapeutic plasma exchange (TPE)** A therapeutic procedure in which blood of the patient is passed through a medical device which separates out plasma from other components of blood. The plasma is removed and replaced with a replacement solution such as colloid solution (e.g., albumin and/or plasma) or a combination of crystalloid/colloid solution.

**Ως θεραπευτική ανταλλαγή πλάσματος (TPE)** ορίζεται η διαδικασία κατά την οποία το αίμα του ασθενούς περνά από μία ιατρική συσκευή, η οποία διαχωρίζει το πλάσμα από τα υπόλοιπα συστατικά του αίματος. Το πλάσμα απομακρύνεται και αναπληρώνεται από διαλύματα αναπλήρωσης, όπως είναι τα κολλοειδή ή συνδυασμό κρυσταλλοειδών/κολλοειδών διαλυμάτων





## TPE - Therapeutic Plasma Exchange





## Βασικοί στόχοι της θεραπευτικής ανταλλαγής πλάσματος (ΤΡΕ)

- ⦿ Απομάκρυνση παθογενετικών μακρομορίων από την κυκλοφορία
- ⦿ Μείωση των επιπέδων κυκλοφορούντων παθολογικών μορίων με σκοπό τη βελτίωση της πορείας της νόσου
- ⦿ Εμπλουτισμό συστατικών του πλάσματος, με τη χρησιμοποίηση πλάσματος ως υγρού αντικατάστασης για να δράσουν άλλες φαρμακευτικές αγωγές
- ⦿ Αναπλήρωση συστατικών του πλάσματος



# Αποτελεσματικότητα της θεραπευτικής ανταλλαγής πλάσματος (ΤΡΕ)

## Εξαρτάται:

- Όγκο πλάσματος που απομακρύνεται σε αναλογία με τον ολικό όγκο πλάσματος
- Κατανομή μεταξύ ενδο και εξωαγγειακού χώρου του παθολογικού παράγοντα προς απομάκρυνση
- Ταχύτητα με την οποία ο παράγοντας ισορροπεί μεταξύ των διαμερισμάτων
- Ρυθμός σύνθεσης του





## Χαρακτηριστικά θεραπευτικής ανταλλαγής πλάσματος (ΤΡΕ)

Αποτελεί μία μη-εκλεκτική μέθοδο απομάκρυνσης παθολογικών πρωτεϊνών του πλάσματος

**Περιορισμοί της μεθόδου:**

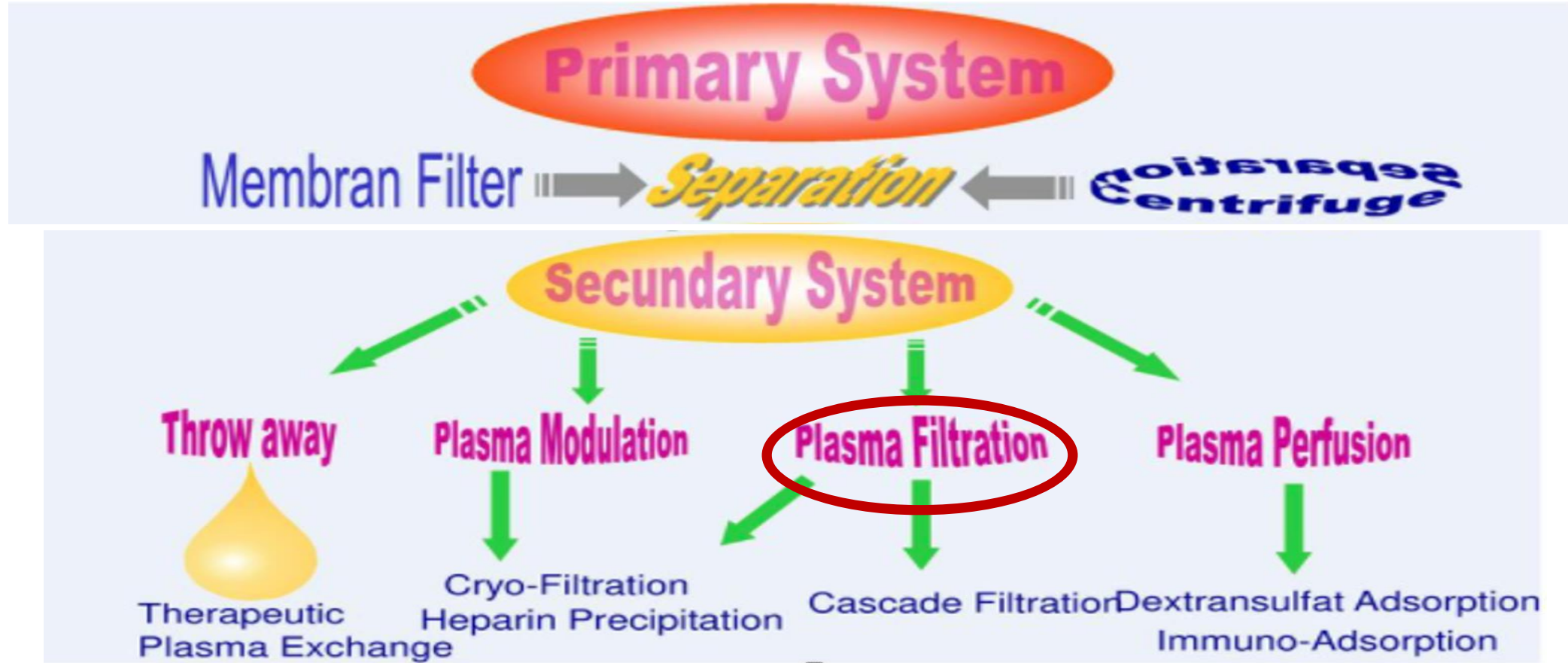
- ❖ Απομάκρυνση όχι μόνο των παθολογικών πρωτεϊνικών μορίων, που συνήθως είναι παρόντα σε μικρές ποσότητες, αλλά και μεγάλων ποσοτήτων φυσιολογικών και χρήσιμων πρωτεϊνών (αλβουμίνη, ανοσοσφαιρίνες, παράγοντες πήξης)
- ❖ Απαίτηση σημαντικού όγκου υγρών αντικατάστασης, με κίνδυνο πρόκλησης αλλεργικών αντιδράσεων ή ιογενών λοιμώξεων

# Ανάγκη εκλεκτικών μεθόδων πλασμαφαίρεσης

Όστε:

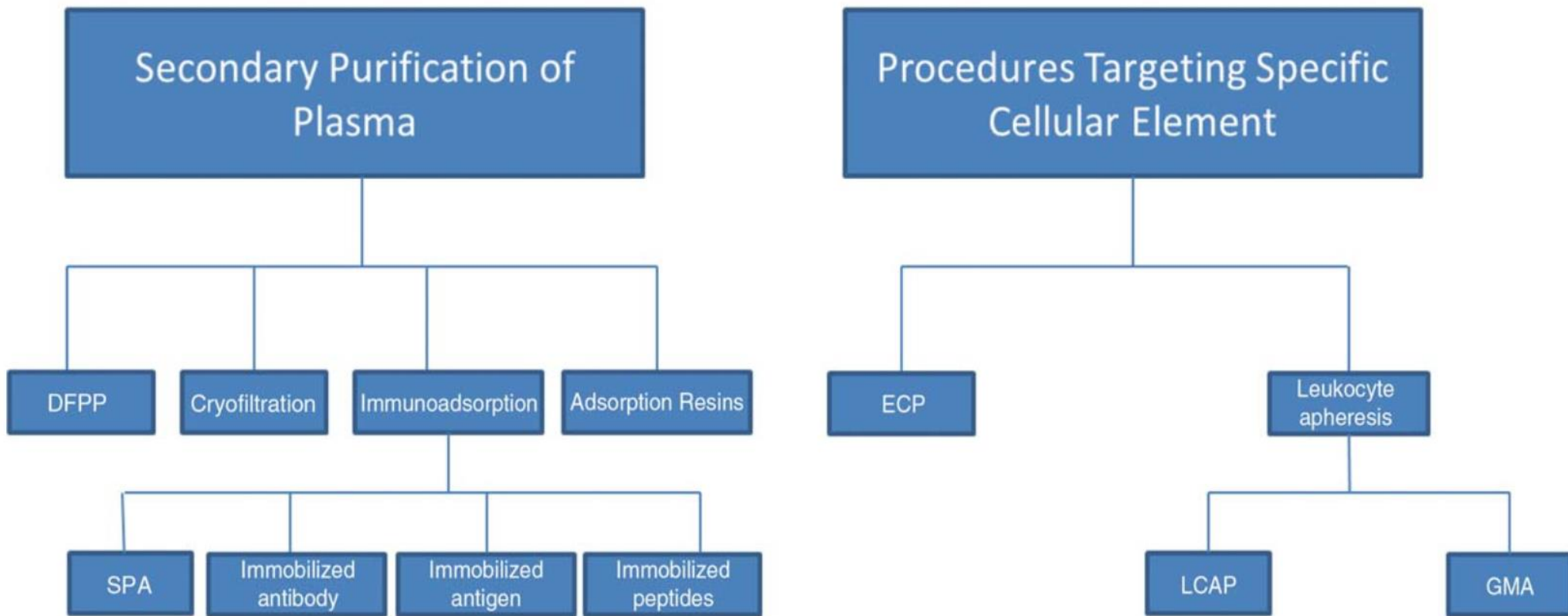
να απομακρύνεται στοχευμένα το/α παθογόνο/α μόριο/α, διατηρώντας σε μεγάλο ποσοστό ανέπαφες τις μη-παθογόνες πρωτεΐνες

Να επιτυγχάνεται καθαρισμός μεγάλων όγκων πλάσματος, χωρίς να απαιτείται υγρό αναπλήρωσης, μειώνοντας έτσι τον κίνδυνο ανεπιθύμητων ενεργειών



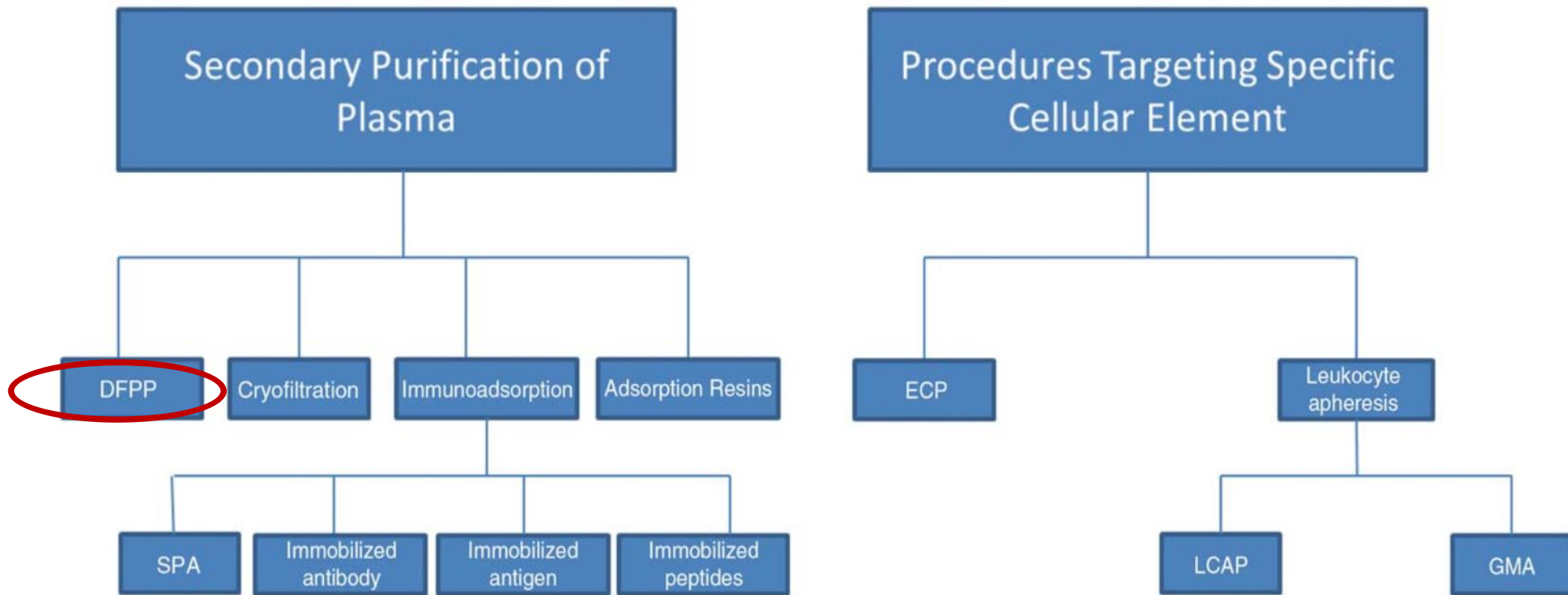


## Selective Apheresis Procedures





## Selective Apheresis Procedures





## Ορισμός DFPP

Double filtration  
plasmapheresis (DFPP)

A filter based therapeutic procedure that removes pathogenic substances from separated plasma based on their size, which is mainly determined by molecular weight and three-dimensional configuration (e.g., autoantibodies, immune complexes, lipoproteins, etc.), by using plasma filters with different pore sizes.

Ως **Πλασμαφαίρεση Διπλής Διήθησης (Double Filtration Plasmapheresis-DFPP ή Cascade Filtration)** ορίζεται η θεραπευτική διαδικασία που απομακρύνει παθογενετικές ουσίες από το ήδη διαχωρισμένο πλάσμα, χρησιμοποιώντας δεύτερο φίλτρο διαχωρισμού, που ανάλογα με το μέγεθος των πόρων της μεμβράνης που διαθέτει, διαχωρίζει τα τμήματα του πλάσματος με βάση το μέγεθος τους, όπως αυτό καθορίζεται από το μοριακό βάρος και την τρισδιάστατη διαμόρφωσή τους. Στην αρχή της DFPP βασίζεται και η **Ρεοαφαίρεση**, μέθοδος που με το δεύτερο φίλτρο δύναται να μειώσει το ιξώδες του αίματος, σε ασθένειες με διαταραχή της μικροκυκλοφορίας

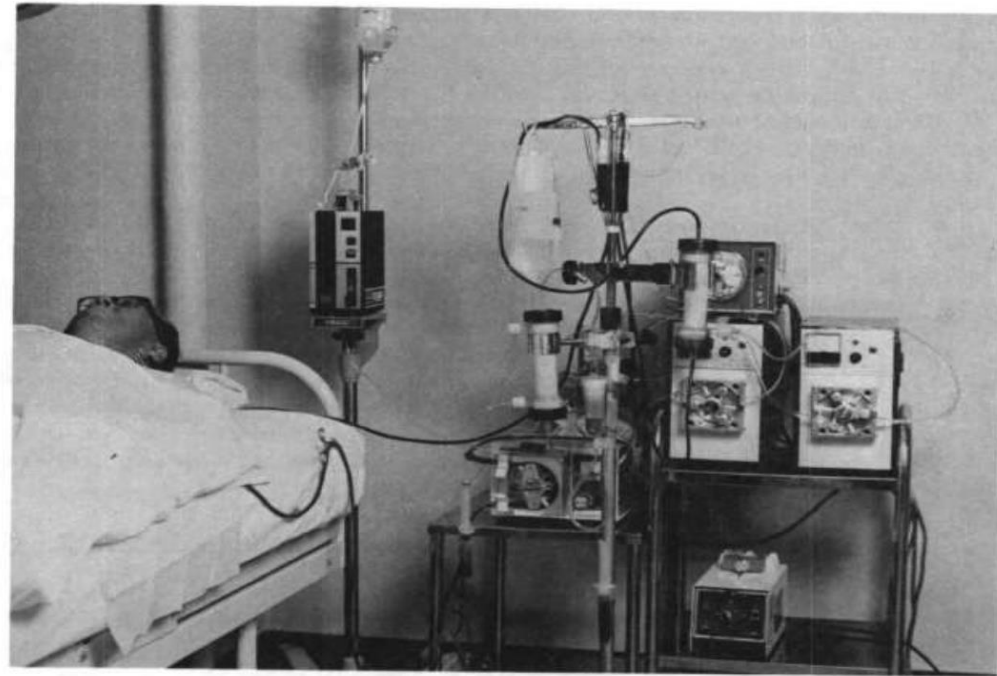


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DOUBLE FILTRATION PLASMAPHERESIS

T. Agishi, I. Kaneko, Y. Hasuo, Y. Hayasaka, T. Sanaka, K. Ota,  
H. Amemiya, N. Sugino, M. Abe\*, T. Ono\*, S. Kawai<sup>†</sup>, and T. Yamane<sup>†</sup>

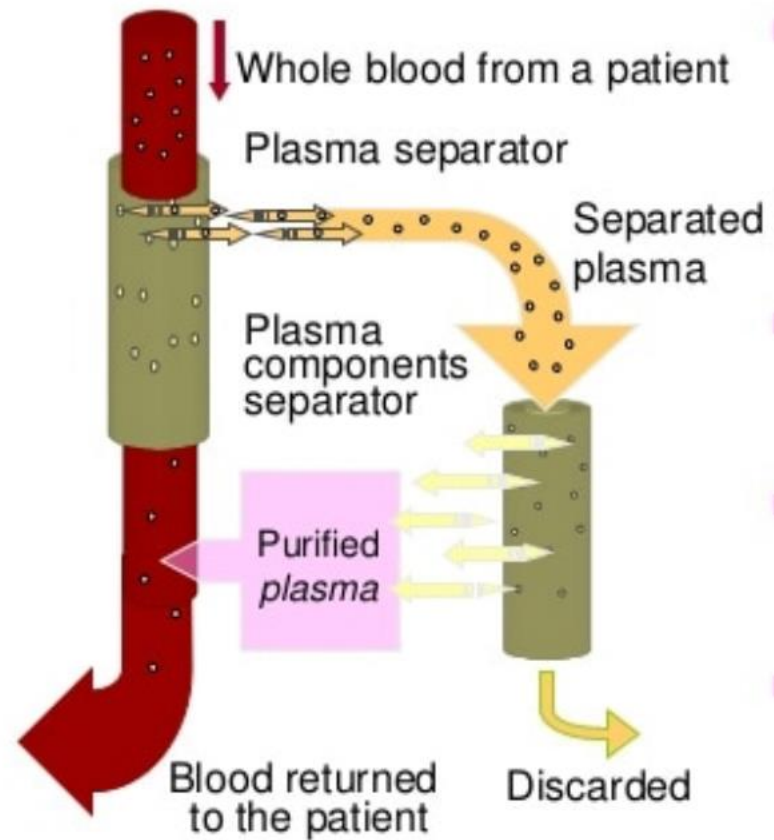
Figure 2. Clinical performance of double filtration plasmapheresis. A plasma separator is positioned on the right and a plasma filter is on the left.





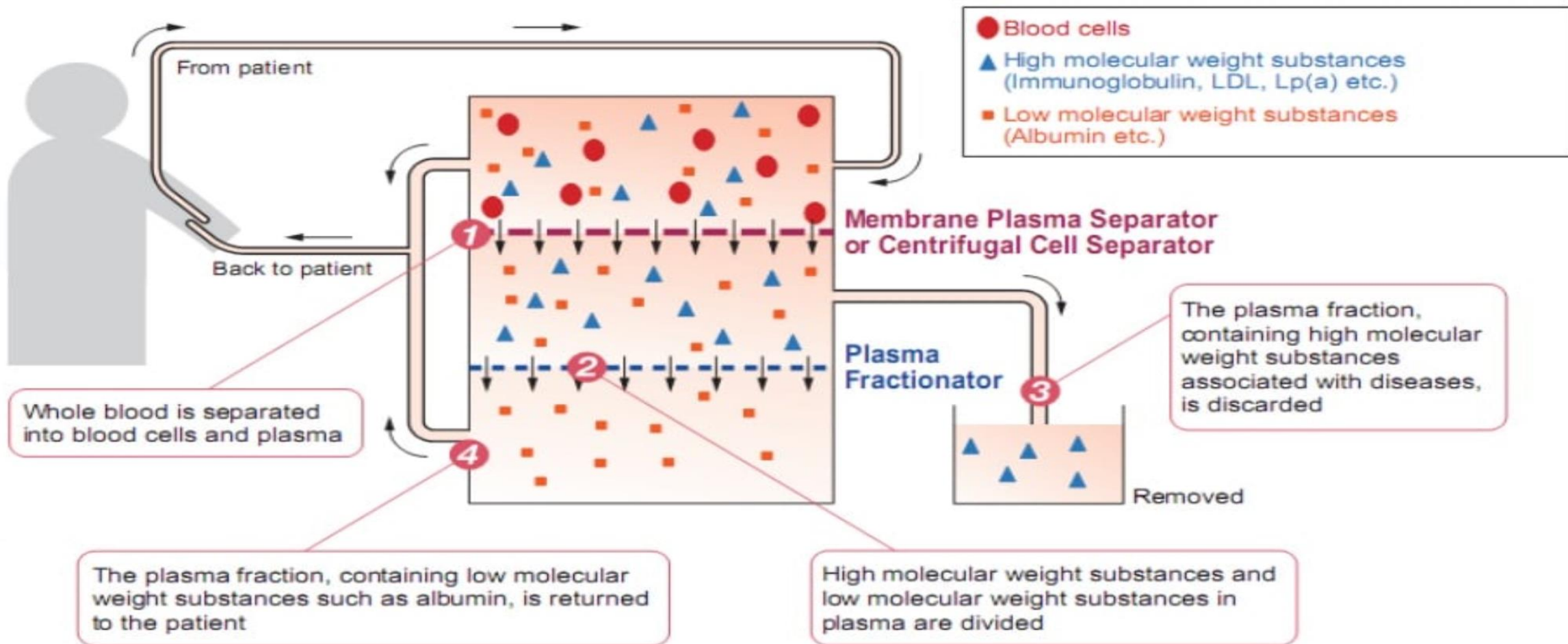
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## Αρχή λειτουργίας





# Αρχή λειτουργίας



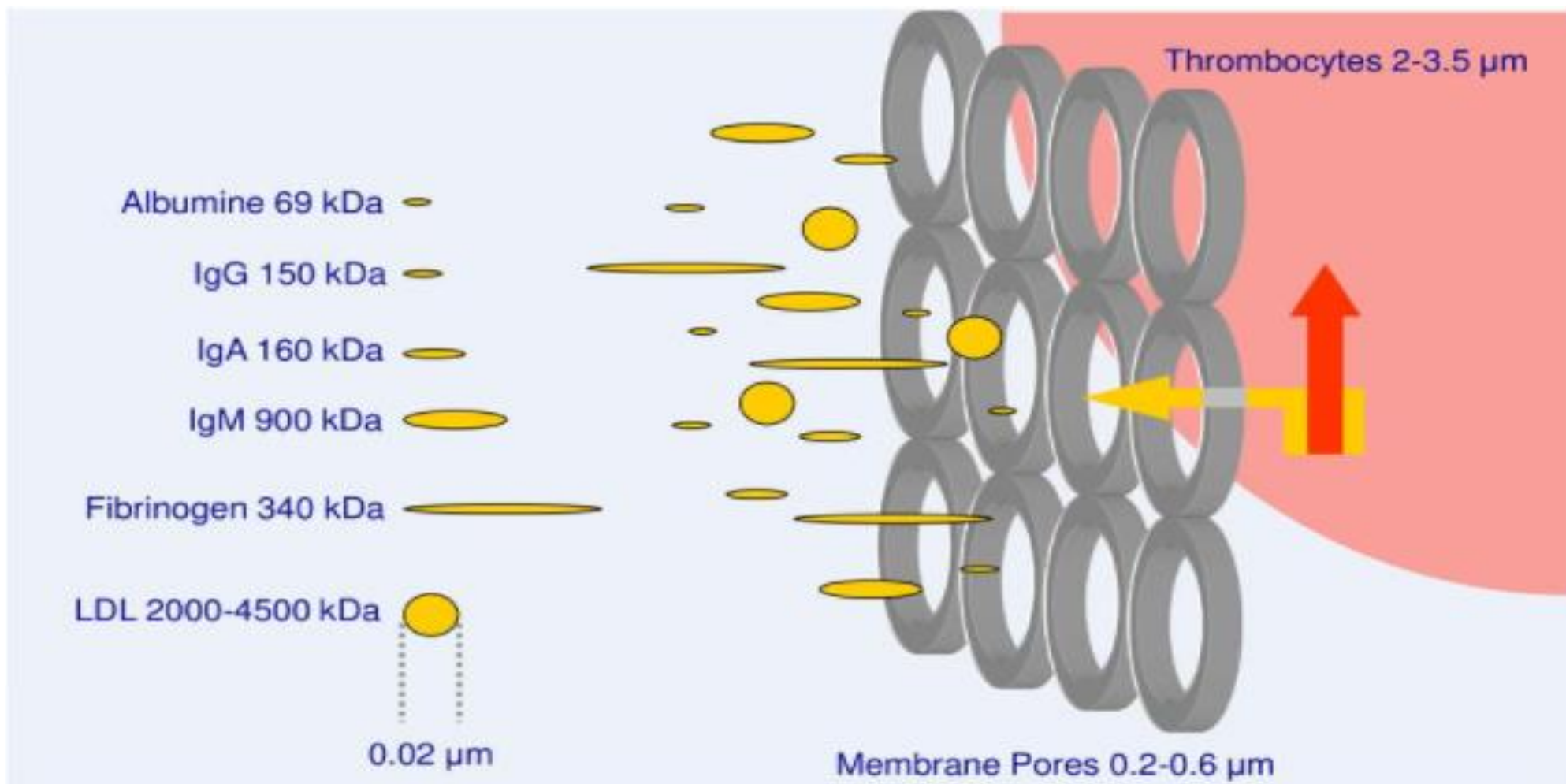
# Μεταβολικά χαρακτηριστικά πρωτεϊνών πλάσματος

Protein	Concentration in plasma (mg/mL)	% intravascular	Change in catabolism with decrease conc.	Molecular weight (kDa)
IgG	12.1	45	Decrease	150
IgA	2.6	42	Constant	160
IgM	0.9	76	Constant	950
IgD	0.2-6.02	75	Increase	175
IgE	0.0001	41	Increase	190
Albumin	42	40	Decrease	66
Fibrinogen	2-4	80	Constant	340
C3	1.5	53		240
A2 macroglobulin		100	constant	820



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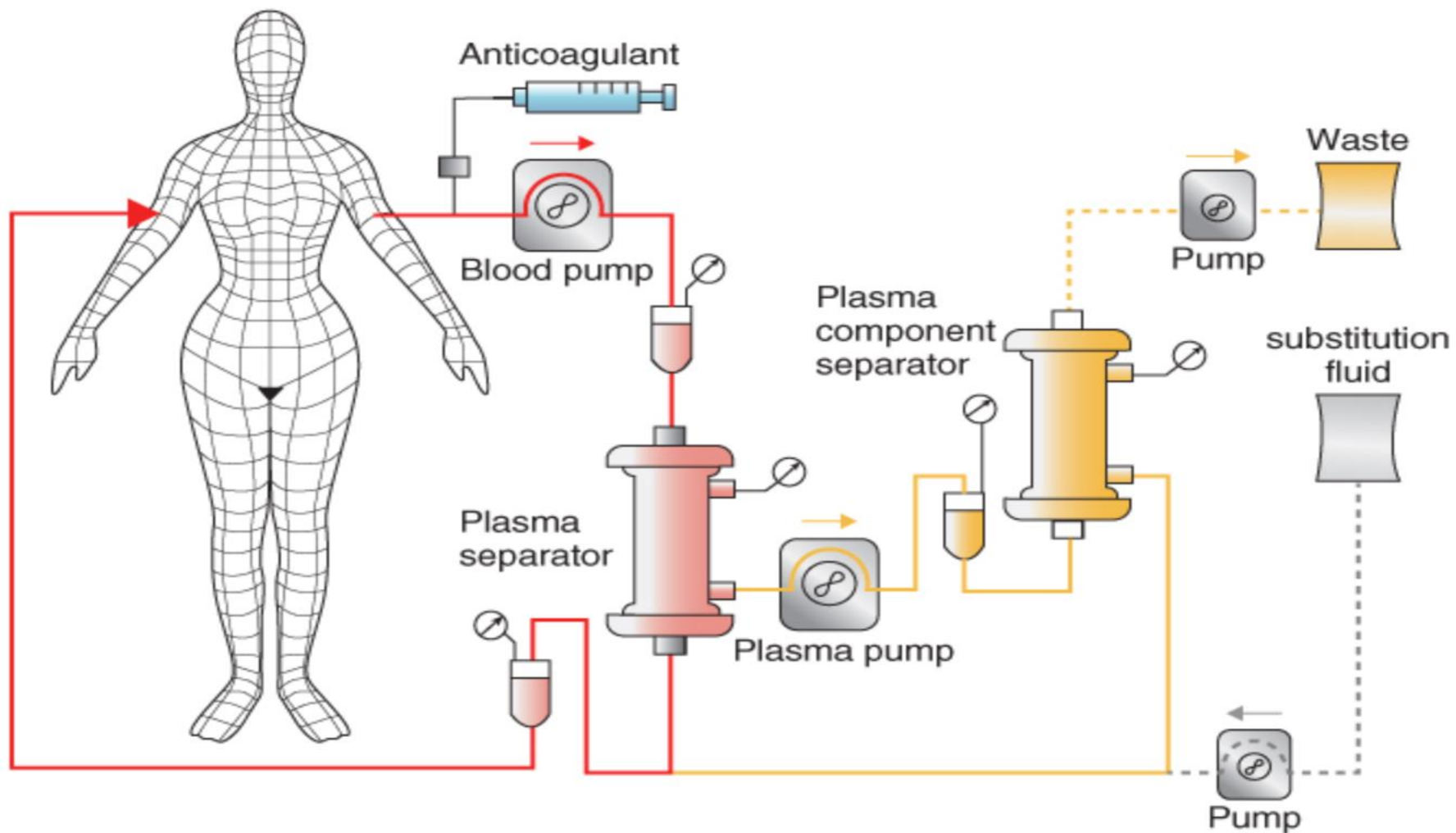
# Αρχή λειτουργίας





ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΑΙΜΑΦΑΙΡΕΣΗΣ

# Κύκλωμα DFPP





ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΑΙΜΑΦΑΙΡΕΣΗΣ

## Συνθήκες Θεραπείας

- ❖ Ρυθμός ροής αίματος (QB): 60-100ml/min
- ❖ Ρυθμός ροής πλάσματος (Qp): 10-50ml/min
- ❖ Ρυθμός διήθησης (QF): περίπου  $QB \times 0,3$  ml/min
- ❖ Ρυθμός ροής απορρίμματος (QD): περίπου  $QF \times 0,1$  ml/min
- ❖ Χειριζόμενος όγκος πλάσματος: 3000-5000 ml
- ❖ Υγρό αντικατάστασης: διαλύματα αλβουμίνης
- ❖ Αντιπηκτικό: ηπαρίνη (κλασική ή ΧΜΒ)
- ❖ Συνεχής παρακολούθηση της διαμεμβρανικής πίεσης φίλτρου (TMP2): ανώτερο επιτρεπόμενο όριο 66.6kPa



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## Αποβαλλόμενος όγκος πλάσματος – υγρό αναπλήρωσης

Type of Cascadeflo EC/ER	Substitution fluid
EC-20W	Discard 10 to 20% of processed plasma volume Substitution with albumin solution (5 to 12.5%)
EC-30W	
ER-4000, EC-40W	
EC-50W	No or saline solution



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## Τεχνικά χαρακτηριστικά

Plasma Separator



**Plasmaflo OP**

Plasma Component  
Separator /  
Col



**Cascadeflo EC**



ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΑΙΜΑΦΑΙΡΕΣΗΣ

## Τεχνικά χαρακτηριστικά

- **Cascaderflo™ EC** (Asahi Kasei Medical, Tokyo Japan):  
4 μοντέλα με διαφορετικό μέγεθος πόρων (20W, 30W, 40W, 50W)

Cascaderflo EC Series



- **Evaflux™** (Kawasumi Laboratories, Tokyo Japan):  
4 μοντέλα με διαφορετικό μέγεθος πόρων (2A, 3A, 4A, 5A)





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# Τεχνικά χαρακτηριστικά

## Specifications Cascadeflo EC Series

	EC-20W	EC-30W	EC-40W	EC-50W
Hollow fiber Material	Ethylene vinyl alcohol copolymer			
Inside diameter	175μm			
Wall thickness	40μm			
Surface area	2.0m <sup>2</sup>			
Pore size (estimated)	0.01μm	0.02μm	0.03μm	<b>0.03μm</b>
Priming volume	150mL			
Container Material	Polycarbonate			
Dimension	280 mm L x 57 mm D			
Sterilization	Gamma-ray			

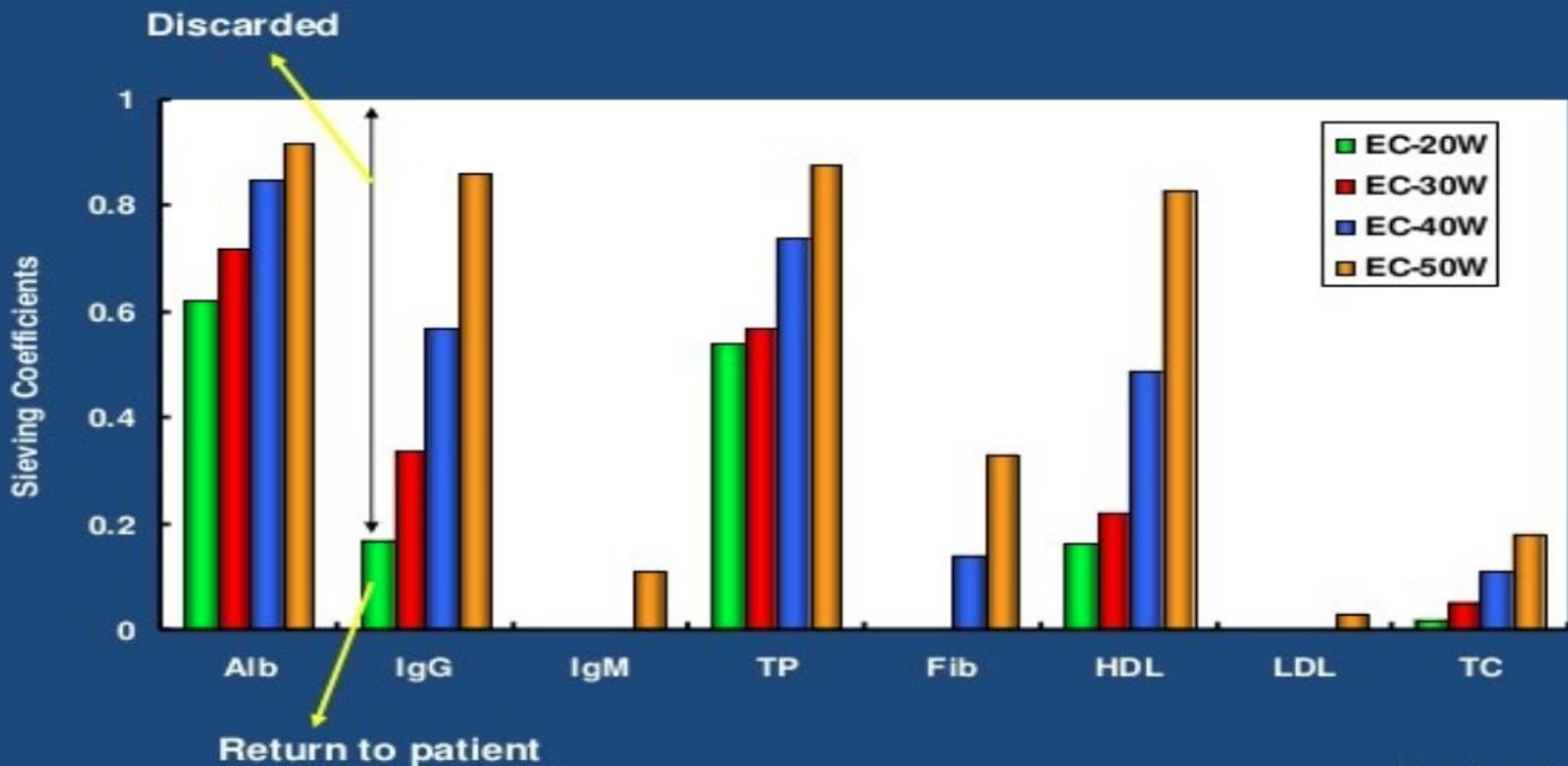
EC-50W has larger pore size than EC-40W, although when pore size is expressed to two places of decimals by half adjust, pore size of EC-40W and EC-50W are same as 0.3μm.



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# Τεχνικά χαρακτηριστικά

## Sieving Coefficient (SC)



In-vivo data



# Τεχνικά χαρακτηριστικά

## Specifications

	Model	2A20	3A20	4A20	5A20
Hollow Fiber	Material	Ethylene vinyl alcohol copolymer			
	Inner diameter	175 (μm)			
	Wall thickness	40 (μm)			
Housing	Surface area	2,0 (m <sup>2</sup> )			
	Outer dimension	57 Ø x 280 L (mm)			
	Material	Poly-carbonate resin			
	Priming volume	140 (ml)			
Filled liquid	Sterile water				
Sterilization method	Gamma-ray irradiation				

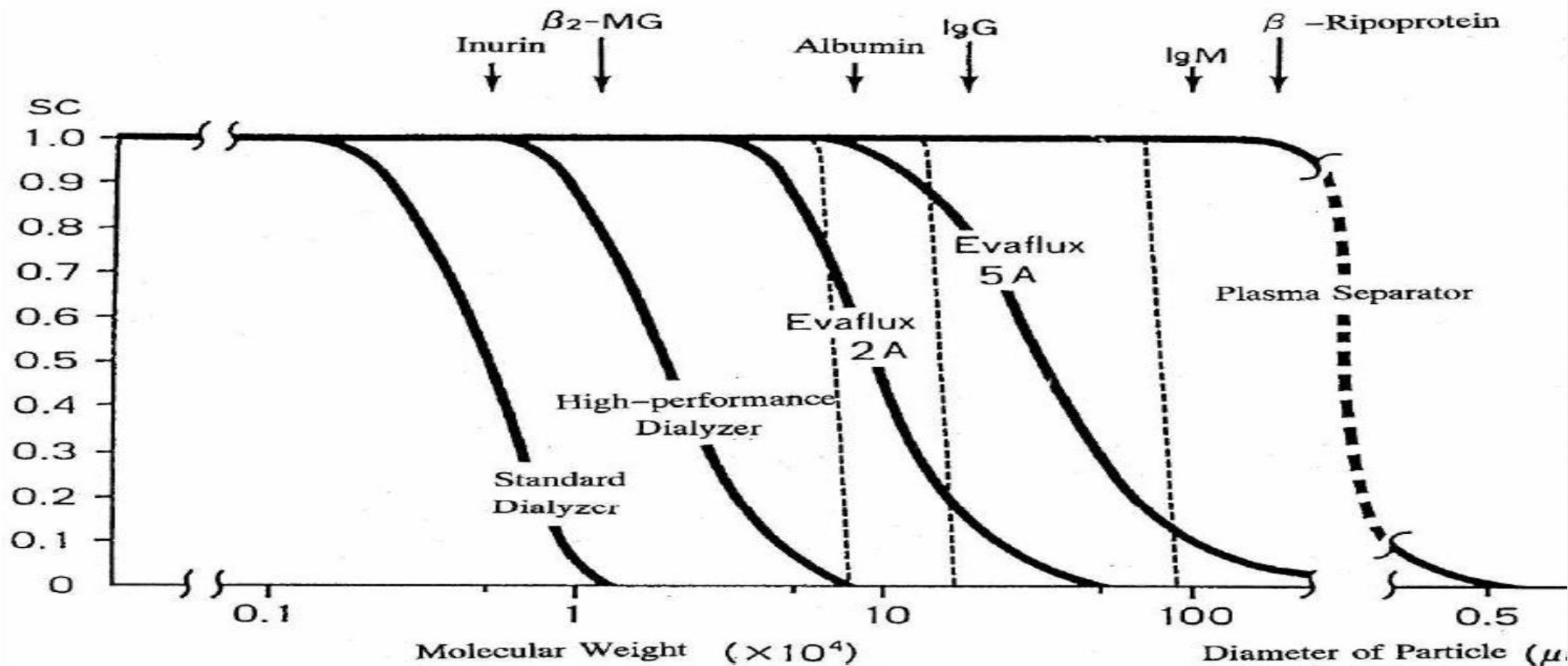




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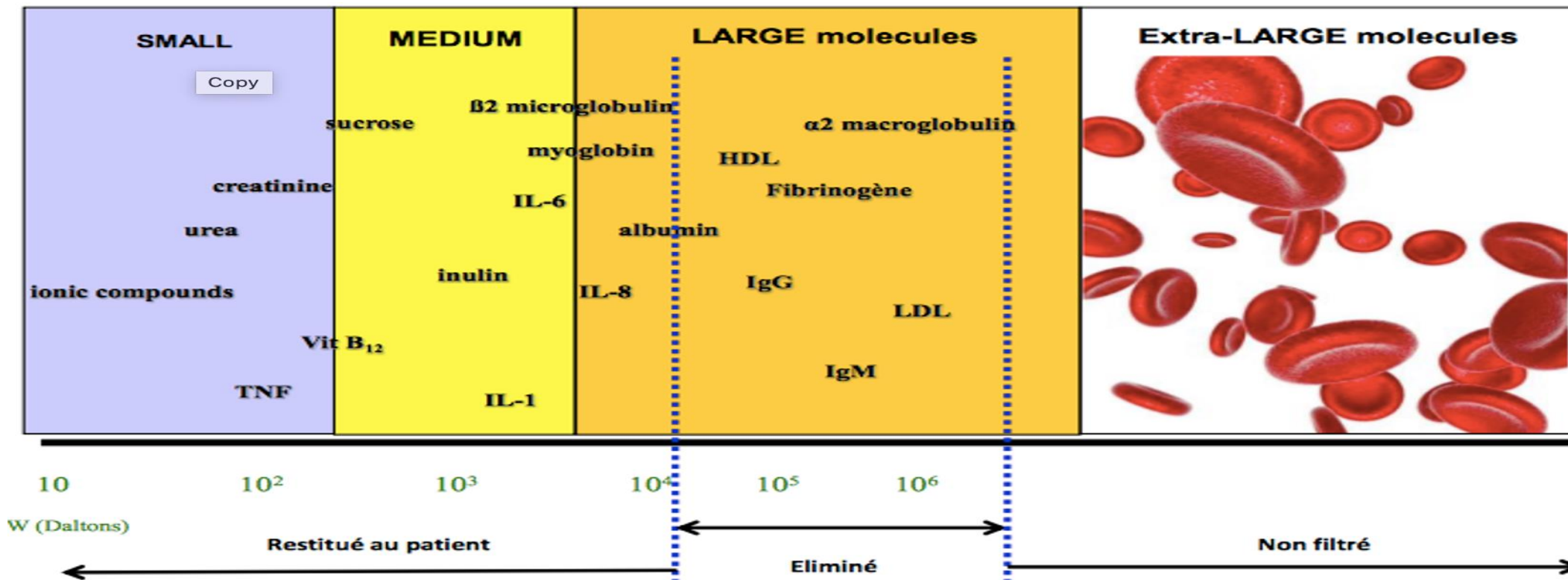
# Τεχνικά χαρακτηριστικά

## Comparison of Membrane Specification





# Τεχνικά χαρακτηριστικά



Ανάλογα με την ένδειξη, δηλαδή την ουσία που επιθυμούμε να απομακρύνουμε (π.χ ανοσοσφαιρίνη, λιποπρωτεΐνες κλπ) και τα χαρακτηριστικά της, επιλέγουμε στο δεύτερο φίλτρο τη μεμβράνη με το κατάλληλο μέγεθος πόρων



## Τεχνικά χαρακτηριστικά

Filter	Pore size ( $\mu\text{m}$ )	Surface area ( $\text{m}^2$ )	Membrane type	Agent removed
Evalfux 2A (Kuraray, Osaka, Japan)	0.01	2.0	Ethylene vinyl alcohol	IgG, IgA
Evaflux 3A (Kuraray)	0.02	2.0	Ethylene vinyl alcohol	Cytokines
Evaflux 4A (Kuraray)	0.03	2.0	Ethylene vinyl alcohol	IgM, LDL
Evaflux 5A (Kuraray)	0.04	2.0	Ethylene vinyl alcohol	LDL-C
Cryoglobulin filter (Pall Gelman, Ann Arbor, MI, U.S.A.)	4.3	0.135	Versapor acrylic copolymer	Cryoproteins
Plasmaflo-AP06M (Asahi, Tokyo, Japan)	0.20	0.65	Cellulose diacetate	Cryoproteins

Ig: immunoglobulin, LDL: low-density lipoprotein, LDL-C: low-density lipoprotein cholesterol.



# Ενδείξεις

## Choice of cascade filter

Indication	Choice
ABO/HLA-incompatible kidney transplantation ABO/HLA-incompatible liver transplantation Antibody mediated rejection (AMR)	EC-20W, 30W
Pemphigus, Pemphigoid	EC-30W
Neurological diseases (e.g., MG, GBS, CIDP, MS) Systemic lupus erythematosus (SLE), Rheumatoid arthritis	EC-30W
Microcirculation Disorders	ER-4000
Familial hypercholesterolemia	EC-50W



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## Συμπερασματικά....

Αποτελεί μία ήμι-εκλεκτική μέθοδο πλασμαφαίρεσης που βασίζεται στην τεχνική της διπλής διήθησης

•Ο ρόλος της είναι η απομάκρυνση του νοσηρού παράγοντα όταν αυτός είναι ουσία μεγάλου ΜΒ, χρησιμοποιώντας ειδικές μεμβράνες για την απομάκρυνση συγκεκριμένων παθογόνων

✓ Ανοσοσφαιρίνες (IgA, IgG, IgM)

✓ Ανοσοσυμπλέγματα (ANCAs, Anti-GBM Abs, Anti-AchR Abs, Anti-ADAMTS13 Abs)

✓ Παθολογικές πρωτεΐνες του πλάσματος

✓ Ινωδογόνο

✓ LDL, Lp(a), VLDL

✓ Ιός ηπατίτιδας C

•Αυτές οι νέες τεχνικές παρέχουν τη δυνατότητα εξατομικευμένης παρέμβασης ανάλογα με τη φύση του εκάστοτε προβλήματος, είναι όμως πολύπλοκες και κοστοβόρες



ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΑΙΜΑΦΑΙΡΕΣΗΣ

## Κλινικές εφαρμογές

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

**Anand Padmanabhan<sup>1</sup> | Laura Connelly-Smith<sup>2</sup> | Nicole Aqui<sup>3</sup> | Rasheed A. Balogun<sup>4</sup> |  
Reinhard Klingel<sup>5</sup> | Erin Meyer<sup>6</sup> | Huy P. Pham<sup>7</sup> | Jennifer Schneiderman<sup>8</sup> |  
Volker Witt<sup>9</sup> | Yanyun Wu<sup>10</sup> | Nicole D. Zantek<sup>11</sup> | Nancy M. Dunbar<sup>12</sup> |**

**Guest Editor: Joseph Schwartz<sup>13</sup>**

# Κλινικές εφαρμογές

## CRYOGLOBULINEMIA

<b>Incidence:</b> About 50% of patients with chronic HCV	<b>Indication</b>	<b>Procedure</b>	<b>Recommendation</b>	<b>Category</b>
	Severe/symptomatic	TPE	Grade 2A	II
	Severe/symptomatic	IA	Grade 2B	II
<b># reported patients:</b> >300	<b>RCT</b>	<b>CT</b>	<b>CS</b>	<b>CR</b>
TPE	1(57)	0	24(302)	NA
IA	1(17)	0	1(4)	0

### Rationale for therapeutic apheresis

TPE removes cryoglobulins efficiently with CRs and CS suggesting improvement in 70-80% of treated patients. It has been used mostly in active moderate to severe cryoglobulinemia with renal impairment (membranoproliferative glomerulonephritis), neuropathy, arthralgia and/or ulcerating purpura. TPE can be performed either alone or in conjunction with immunosuppressive therapy and has been used in both short- and long-term management.

Double or cascade filtration, which separates plasma out of whole blood in the first filter and removes high molecular weight proteins in the second filter (such as IgM), has also been used to treat cryoglobulinemia. Another apheresis modality used in this disease is cryofiltration or cryoglobulinapheresis, which cools the plasma in an extracorporeal circuit either continuously or in a 2-step procedure to remove cryoglobulins; the remaining plasma is warmed to body temperature prior to returning to the patient. Cryofiltration is less efficient at removing cryoglobulins than DFPP. In a randomized, parallel group study IA apheresis confirmed to be effective for lowering cryoglobulins (Stefanutti, 2009). This study was the lone RCT that included IA apheresis as in the intervention group in all 10 studies that met the selection criteria in a database systematic review (Montero, 2018).

# Κλινικές εφαρμογές

## HYPERVISCOSITY IN HYPERGAMMAGLOBULINEMIA

Incidence: 5/1,000,000/yr	Indication	Procedure	Recommendation	Category
	Symptomatic	TPE	Grade 1B	I
	Prophylaxis for rituximab	TPE	Grade 1C	I
<b># reported patients: &gt;300</b>	<b>RCT</b>	<b>CT</b>	<b>CS</b>	<b>CR</b>
Symptomatic	0	3(46)	21(279)	NA
Prophylaxis for rituximab	0	0	3(45)	3(3)

### Rationale for therapeutic apheresis

TPE has been successfully used since the late 1950s and has been shown to promptly reverse retinopathy and other clinical manifestations of HVS. IgM is 80% intravascular and serum viscosity rises steeply with increasing IgM levels. Thus, a relatively small reduction in IgM concentration has a significant effect on lowering serum viscosity. TPE reduces viscosity 20-30% per treatment.

### Technical notes

Conventional calculations of plasma volume based on weight and hematocrit are inaccurate in M-protein disorders because of plasma volume expansion. Cascade filtration and membrane filtration techniques have been described and may have similar efficacy in removing M-protein.

# Κλινικές εφαρμογές

## FAMILIAL HYPERCHOLESTEROLEMIA

Prevalence: Heterozygotes: 1/200-300; Homozygotes: 1-6/1,000,000	Indication	Procedure	Recommendation	Category
	Homozygotes	LA	Grade 1A	I
	Heterozygotes	LA	Grade 1A	II
	Homozygotes/Heterozygotes	TPE	Grade 1B	II
# reported patients: >300	RCT	CT	CS	CR
LA	4(207)	10(609)	NA	NA
TPE	0	1(10)	14(62)	NA

### Technical notes

Selective LA systems reduce LDL-C levels by >60-70% after a single session. For children with body weights of 10-20 kg, experiences with selective LA systems like plasma DSA or DFPP exist (Klaus, 2018). Priming the extracorporeal circuit with blood or plasma products might be considered. Angiotensin converting enzyme inhibitors are contraindicated with adsorption-based LA due to increased bradykinin generation, leading to profound hypotension. Monitoring of hemoglobin, ferritin, transferrin saturation is recommended along with iron supplementation for the prevention of anemia with long-term LA.

# Κλινικές εφαρμογές

## HYPERTRIGLYCERIDEMIC PANCREATITIS

<b>Incidence:</b> 18/100,000/yr	<b>Indication</b>	<b>Procedure</b>	<b>Recommendation</b>	<b>Category</b>
	Severe HTG-AP	TPE/LA	Grade 1C	III
	Prevention of HTG-AP relapse	TPE/LA	Grade 2C	III
<b># reported patients:</b> >300	<b>RCT</b>	<b>CT</b>	<b>CS</b>	<b>CR</b>
TPE/LA	0	3(66)	29(286)	NA

HTG-AP = hypertriglyceridemic acute pancreatitis

### Technical notes

Efficacy of membrane plasma separation for TPE can be impaired with chylomicronemia, so that use of centrifugal plasma separation is necessary. The use of LA techniques was successfully described (e.g., DFPP, dextran-sulfate adsorption from whole blood). However, these systems are optimized for the elimination of small to mid-sized apoB100-positive lipoproteins and efficacy can be reduced with chylomicronemia. According to its effect on LPL activity, heparin has been suggested as standard anticoagulant for these procedures. However, many reports have used ACD-A with similar TG reductions. Albumin was mostly used as the replacement fluid. Some have used plasma as it contains LPL and could enhance TG removal. No direct comparisons of replacement fluids have been reported.

# Κλινικές εφαρμογές

## LIPOPROTEIN(a) HYPERLIPOPROTEINEMIA

Prevalence: $\approx$ 20% Lp(a) levels >50 mg/dl	Indication	Procedure	Recommendation	Category
	Progressive ASCVD	LA	Grade 1B	II
# reported patients: >300	RCT	CT	CS	CR
	3(61)	3(283)	NA	NA

ASCVD = atherosclerotic cardiovascular disease, Lp(a) = Lipoprotein(a)

### Technical notes

Angiotensin converting enzyme (ACE) inhibitors are contraindicated in patients undergoing adsorption-based LA due to increased bradykinin generation, leading to profound hypotension.

**Volume treated:** Plasma or whole blood volumes vary according to recommendations of device manufacturers.

**Frequency:** Once every 1-2 weeks

**Replacement fluid:** NA

# Κλινικές εφαρμογές

## AGE RELATED MACULAR DEGENERATION, DRY

<b>Prevalence:</b> 2% (dry AMD and soft drusen, US population)	<b>Indication</b>	<b>Procedure</b>	<b>Recommendation</b>	<b>Category</b>
	High-risk	Rheopheresis	Grade 2B	II
<b># reported patients:</b> >300	<b>RCT</b>	<b>CT</b>	<b>CS</b>	<b>CR</b>
	6(433)	3(396)	NA	NA

### Rationale for therapeutic apheresis

Rheopheresis removes rheologically active, high-molecular weight molecules (e.g., fibrinogen, LDL,  $\alpha$ 2-macroglobulin, fibronectin, von Willebrand factor) which may impair the retinal microcirculation or contribute to a chronic inflammatory state. Rheopheresis results in a reduction in blood and plasma viscosity, platelet and red cell aggregation, which may also improve RPE perfusion and function.

### Technical notes

The majority of CS and trials used **DFPP** where plasma is first separated by membrane plasma separation and then passed through a plasma filter of appropriate pore size (rheofilter) where high-molecular weight substances are removed. Centrifugal plasma separation followed by plasma filtration has been alternatively used. Currently, the filtration devices necessary for this treatment are not licensed in the US but are available in Europe, Canada, and Asia.

**Volume treated:** 0.8-1.5 TPV

**Frequency:** 8 to 10 treatments (2/wk) over 8-21 wks

**Replacement fluid:** NA

# Κλινικές εφαρμογές

## SUDDEN SENSORINEURAL HEARING LOSS

Incidence: 15-30/100,000		Procedure		Recommendation	Category
		LA	Rheopheresis	Grade 2A	III
# reported patients: >300	RCT	CT		CS	CR
LA*	4(390)	0		NA	NA
Rheopheresis	1(240)	1(52)		3(43)	NA
TPE	0	0		1(16)	1(1)

\*HELP-apheresis

### Rationale for therapeutic apheresis

Improvement of inner ear microcirculation and hair cell function by acute reduction of fibrinogen and cholesterol levels were the pathogenic mechanisms guiding the approach to use apheresis, in particular HELP-apheresis or rheopheresis as treatment for SSHL. Elevated fibrinogen and LDL cholesterol were identified as pathogenic factors at molecular levels, however, further analysis failed to confirm that thresholds might be helpful for the indication of apheresis.

# Κλινικές εφαρμογές

## PERIPHERAL VASCULAR DISEASES

Prevalence: 3-10% of population (US)		Procedure	Recommendation	Category
		LA	Grade 1B	II
# reported patients: 100-300	RCT	CT	CS	CR
	1(42)	0	7(151)	NA

### Technical notes

Angiotensin converting enzyme (ACE) inhibitors are contraindicated in patients undergoing LA. The columns function as a surface for plasma kallikrein generation which, in turn, converts bradykininogen to bradykinin. Kininase II inactivation of bradykinin is prevented by ACE inhibition resulting in unopposed bradykinin effect, hypotension and flushing. This is not seen with the HELP system.

# Κλινικές εφαρμογές

## TRANSPLANTATION, RENAL, ABO COMPATIBLE

Incidence: AMR: 10%, 40% with desensitization; HLA sensitization: 30%	Indication	Procedure	Recommendation	Category
	AMR	TPE/IA	Grade 1B	I
	Desensitization, LD	TPE/IA	Grade 1B	I
	Desensitization, DD	TPE/IA	Grade 2C	III
<b># reported patients: &gt;300</b>	<b>RCT</b>	<b>CT</b>	<b>CS</b>	<b>CR</b>
AMR	3(61)	8(342)	NA	NA
Desensitization, LD	0	6(583)	NA	NA
Desensitization, DD	0	0	1(20)	0

AMR = Antibody-mediated rejection; HLA = Human leukocyte antigen; LD = Living donor; DD = Deceased donor

### Rationale for therapeutic apheresis

In AMR, DSA can be removed with TPE, DFPP, and IA. Apheresis is always performed in conjunction with other immunosuppressive drugs. RCTs in the early 1980s did not show TPE to be beneficial when used in combinations with corticosteroids for either acute rejection or acute vascular rejection. CS since 1985 have shown improvement when TPE is used in patients with acute vascular rejection in combination with a variety of anti-rejection medications. This is likely due to improved anti-rejection medications, improved DSA detection, and improved AMR definition using Banff criteria. Previously there was a high graft loss rate with acute vascular rejection; current regimens that include TPE have a graft survival rate of 70-80% (90% in reports with TPE, IVIG, and rituximab).

# Κλινικές εφαρμογές

## TRANSPLANTATION, RENAL, ABO INCOMPATIBLE

<b>Incidence:</b> <1%	<b>Indication</b>	<b>Procedure</b>	<b>Recommendation</b>	<b>Category</b>
	Desensitization, LD	TPE/IA	Grade 1B	I
	AMR	TPE/IA	Grade 1B	II
<b># reported patients:</b> >300	<b>RCT</b>	<b>CT</b>	<b>CS</b>	<b>CR</b>
	0	0	26(911)	NA

LD = live donor; AMR = antibody mediated rejection

### Rationale for therapeutic apheresis

While there are no controlled clinical trials on use of TPE to facilitate ABOi renal transplantation, an abundance of supportive evidence exists. Given that hyperacute rejection and acute antibody mediated rejection are risks in ABOi renal transplants, TPE has been used as key therapeutic modality to reduce anti-A and/or anti-B titers in peri-transplant period with goal of preventing rejection and facilitating graft survival. Both short and long-term ABOi kidney transplant survival statistics compare well with that seen in ABO-compatible transplants. In ABOi kidney transplantation, TPE is used to lower antibody titers below a critical threshold (which differs based on titration method/ technique) prior to the transplant procedure. Apart from TPE, DFPP and ABO-antigen specific and non-specific IA columns have been used (outside the US) to remove ABO antibodies.

# Κλινικές εφαρμογές

## MYASTHENIA GRAVIS

Incidence: 3-28/million	Indication	Procedure	Recommendation	Category
	Acute, short-term treatment*	TPE/IA	Grade 1B	I
	Long-term treatment	TPE/IA	Grade 2B	II
<b># reported patients: &gt;300</b>	<b>RCT</b>	<b>CT</b>	<b>CS</b>	<b>CR</b>
TPE	10(394)	11(545)	NA	NA
IA	1(19)	5(131)	15(164)	NA

\*Treatment recommendations are for moderate-severe disease including myasthenic crisis, unstable or refractory disease, unstable disease activity pre-thymectomy

### Rationale for therapeutic apheresis

There are 3 major mechanisms of action for TPE, or IA in MG: immediate intravascular reduction of autoantibody concentration, pulsed induction of antibody redistribution, and subsequent immunomodulatory changes. Absolute autoantibody levels do not correlate with disease severity. However, a (Mandawat, 2011) IA methods exhibited equal efficacy compared to TPE, thus avoiding replacement of human plasma products with their potential side effects or cost. **DFPP** was comparable to TPE with small pore plasma filters and procedural steps of rinsing, plasma discarding and substitution. TPE, or IA work rapidly, the clinical effect can be apparent within 24 hours but may take a week. Concomitant immunosuppression must be initiated or modified for sustained control of MG activity. Apheresis may be more effective than IVIG in patients with MuSK- MG.

# Κλινικές εφαρμογές

## SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Prevalence: 1-2/1000	Indication	Procedure	Recommendation	Category
	Severe complications	TPE	Grade 2C	II
# reported patients: >300	RCT	CT	CS	CR
Severe complications	1(20)	2(108)	15(148)	NA

### Rationale for therapeutic apheresis

TPE was initially used to treat SLE under the assumption that removing pathogenic autoantibodies and immune complexes would control disease activity. However, the first RCT in mild SLE, where the patients underwent six 4L exchanges within 2 weeks with expected autoantibody and immune complex reduction, showed no clinical improvement (Wol 1983). TPE in LN has been specifically identified as a Grade II (CR) recommendation for SLE associated TTP, myasthenia gravis, hyperviscosity, catastrophic APS, and cryoglobulinemia. There are data on use of IA and DFPP for severe refractory cases. A RCT in severe LN suggested that adjunctive IA and TPE were equally effective in reducing SLEDAI scores (Loo, 2010).

# Κλινικές εφαρμογές

## TOXIC EPIDERMAL NECROLYSIS (TEN)

Incidence: 2/1,000,000/yr	Indication	Procedure	Recommendation	Category
	Refractory	TPE	Grade 2B	III
# reported patients: 100-300	RCT	CT	CS	CR
	0	0	15(172)	NA

### Rationale for therapeutic apheresis

The rationale supporting TPE in TEN includes removal of drug/drug metabolites, cytokines or other mediators of keratinocyte cytotoxicity. At least one report has demonstrated decreased levels of serum cytokines following TPE (Narita, 2011). TPE is typically not used in patients with SJS although there is rare use of TPE for SJS complicated by hepatic encephalopathy.

Numerous uncontrolled CRs and CS have noted use of TPE in the setting of severe cases of TEN refractory to standard treatment. Given the significant heterogeneity in patient condition at the time of initiation of TPE, the number of TPE treatments utilized, different concurrent medications that these patients were on, and varied disease severity, a rigorous evaluation of TPE efficacy in TEN is challenging. All reports describe application of TPE in combination with other therapies.

### Technical notes

While most reports have utilized TPE to treat refractory TEN, some groups from Japan have also used DFPP, which is not available in the US.

# Κλινικές εφαρμογές

## ATOPIC (NEURO-) DERMATITIS (ATOPIC ECZEMA), RECALCITRANT

Incidence: Children: atopic dermatitis 10-30%; adults: 1-3%; recalcitrant: rare	Procedure		Recommendation	Category
	ECP		Grade 2A	III
	IA		Grade 2C	III
	TPE/DFPP		Grade 2C	III
# reported patients: 100-300	RCT	CT	CS	CR
ECP	1(20)	2(45)	9(59)	NA
IA	0	6(100)	1(2)	NA
TPE/DFPP	0	1(9)	0	1(1)

### Rationale for therapeutic apheresis

Given the side effects of third-line therapies including immunosuppressive agents and phototherapies, ECP is used as a non-toxic and non-immunosuppressive alternative. Since 1994, CS and controlled studies in >100 patients have been published with a 70% of patients having a favorable response to ECP, requiring at least 6 cycles for a response. In one RCT, equivalence to cyclosporine therapy was shown (Kopplhus, 2014).

TPE and DFPP are used to reduce IgE and immune complexes from patients' blood. For DFPP, there is one CT showing a significant improvement in symptoms.

### Technical notes

**Volume treated:** ECP: Typically, MNCs are obtained from processing 1.5L of whole blood, but the volume processed may vary based on patient weight and HCT. The 2-process method collects and treats MNCs obtained from processing 2 TBV; IA: 2-4 TPV; TPE and DFPP: 1-2 TPV

**Frequency:** ECP: 1 cycle every 2 weeks for 12 weeks, then tapering; IA: series of up to 3-5 consecutive daily IA every 4 weeks up to 10-12 total; TPE and DFPP: weekly

**Replacement fluid:** TPE/DFPP: Albumin

# Κλινικές εφαρμογές

## PEMPHIGUS VULGARIS

Incidence: <1/100,000/yr (US)	Indication	Procedure	Recommendation	Category
	Severe	TPE	Grade 2B	III
	Severe	ECP/IA	Grade 2C	III
# reported patients: 100-300	RCT	CT	CS	CR
TPE	1(40)	0	8(87)	13(13)
ECP	0	0	1(4)	7(11)
IA	0	1(6)	6(35)	5(5)

### Rationale for therapeutic apheresis

The rationale for using TPE and IA in pemphigus vulgaris treatment is because there are circulating pathogenic autoantibodies. TPE has been utilized in patients with severe symptoms who either received high doses of conventional agents and/or had an aggressive and rapidly progressive disease or treatment resistant. TPE was used in patients in all age groups (13-80 years). The duration of disease prior to TPE use ranged 1 month to 25 years. The TPE goal was to reduce the level of autoantibodies and improve clinical symptoms. In one multicenter RCT patients were randomized into prednisolone alone (n = 18) and prednisolone plus 10 large volume TPE (n = 22) over four weeks (Guillaume, 1988). There were four septic deaths and no steroid sparing effect in TPE arm. IA has been promoted in Europe with increasing number of patients treated and reported clinical responses. Monocentric CRs and CSs showed in the adjuvant setting decrease of the circulating antibodies, which correlated to the improvement of bullous-erosive lesions, and corticoid sparing effect. Selective plasma exchange that uses a selective membrane plasma separator and DFPP have also been tried with some success.

# Κλινικές εφαρμογές

## THYROID STORM

Prevalence: 1/100,000		Procedure	Recommendation	Category
		TPE	Grade 2C	II
# reported patients: 100-300	RCT	CT	CS	CR
	0	0	15(133)	NA

### Rationale for therapeutic apheresis

Both TPE and emergency surgery have been used to treat thyroid storm in patients who respond poorly to first line therapeutic measures. TPE is usually performed in patients with thyroid storm with severe symptoms and when the patient does not improve with first-line therapies within 24-48 hours of treatment or when first-line therapies cannot be used due to toxicity, such as leukopenia due to PTU. Since a portion of T<sub>3</sub> and T<sub>4</sub> is firmly bound to plasma proteins, TPE should, in theory, efficiently reduce their circulating pool and as such, most patients had a decrease in the hormone concentrations. In a review of the literature, TPE decreased the levels of free T4 and T3, and total T3 and T4 significantly (Garla, 2018). In patients with amiodarone-associated thyrotoxicosis, TPE has also been used to reduce the amiodarone plasma concentration, which has a half-life of months in patients on chronic therapy. TPE in this condition is particularly indicated for patients who have no underlying thyroid disease and develop a drug-induced destructive thyroiditis. The therapeutic benefit of TPE can be achieved by removal of potential substances from the thyroid storm such as autoantibodies (Graves' disease), catecholamines (released by the sympathetic system) and cytokines. In rare cases, TPE is used to render the thyrotoxicotic patient euthyroid prior to thyroidectomy. TPE effect is transient and the hormone levels typically rise again the next day. Continuous dialysis modalities, e.g., with albumin containing dialysate, were experimentally used to increase thyroid hormone clearance. If removal of autoantibodies is considered for stabilizing the therapeutic result, in particular with associated ophthalmopathy, selective apheresis methods like IA or DFPP have been used.

# Κλινικές εφαρμογές

## VASCULITIS, IgA (HENOCH-SCHÖNLEIN PURPURA)

Incidence: 13-22/100,000 with 1% developing RPGN	Indication	Procedure	Recommendation	Category
	Crescentic RPGN	TPE	Grade 2C	III
	Severe extrarenal manifestations	TPE	Grade 2C	III
# reported patients: <100	RCT	CT	CS	CR
	0	0	9(72)	22(25)

### Rationale for therapeutic apheresis

The rationale for TPE is the removal of IgA1-containing immune complexes or IgG autoantibodies. Early positive experiences of the use of TPE in treating some forms of RPGN resulted in the application of TPE to HSP when crescentic glomerulonephritis developed in the disease. In addition, because of the use of TPE to treat severe sequelae of other forms of vasculitis, TPE has also been used to treat severe GI or skin manifestations and cerebritis in HSP. Numerous CRs have demonstrated some success in severely ill patients with IgAV or IGAVN and severe bleedings of the lung, GI tract and in cerebritis.

Limited but encouraging data suggest TPE may benefit patients with severe disease. Seven CRs and 8 CS totaling 67 patients have examined the use of TPE in treating CreIgAVN in the setting of HSP. In 27 of these patients, concurrent immunosuppressive therapy was not given. In these patients treated with only TPE, 21 had complete resolution of their renal disease, 2 had persistent hematuria, 1 had persistent proteinuria, and 2 progressed to ESRD. The remaining patient was an adult who had resolution of renal disease with TPE but recurrence following discontinuation of TPE. The patient subsequently had complete resolution of renal disease with TPE and cyclophosphamide. Of the 40 patients treated with TPE and corticosteroids and/or immunosuppressants, all were reported to have had resolution of renal disease.

### Technical notes

Replacement fluid has varied depending upon the clinical situation with the final portion consisting of plasma in the presence of severe bleeding. DFPP has also been used in a single patient with RPGN in HSP with resolution of renal disease (Chen, 2004).

# Κλινικές εφαρμογές

Table 1. List of diseases that DFPP is National Health Insurance covered as of April 2020.

Neurological Disorders	Myasthenia gravis (MG)
	Guillain-Barré syndrome (GBS)
	Chronic inflammatory demyelinating polyneuropathy (CIDP)
	Multiple sclerosis (MS)
Rheumatic Disorders	Systemic lupus erythematosus (SLE)
	Malignant rheumatoid arthritis (MRA)
	Kawasaki disease
Metabolic Disorders	Familial hypercholesterolemia (FH)
Organ Transplantations	ABO/HLA incompatible kidney transplant
	ABO/HLA incompatible liver transplant
Renal Disorders	Anti-glomerular basement membrane (GBM) antibody mediated rapidly progressive glomerulonephritis (RPGN)
	Anti-neutrophil cytoplasm autoantibody (ANCA) mediated RPGN
	Focal segmental glomerulosclerosis (FSGS)
Hematological Disorders	Thrombotic thrombocytopenic purpura (TTP)
	Hemolytic uremic syndrome (HUS)
	Multiple myeloma (MM)
	Macroglobulinemia
	Hemophilia with inhibitor
Hepatic Disorders	Chronic hepatitis C
	Acute hepatic failure
	Postoperative hepatic failure
Dermatologic Disorders	Pemphigus vulgaris
	Pemphigoid
	Toxic epidermal necrolysis (TEN)
	Stevens-Johnson syndrome
Others	Arteriosclerosis obliterans (ASO)
	Severe blood-type incompatible pregnancy



ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΑΙΜΑΦΑΙΡΕΣΗΣ

## Προοπτική ....

Case report

### Successful treatment of positive-sense RNA virus coinfection with autoimmune hepatitis using double filtration plasmapheresis

Kamimura H, Kamimura K, Tsuchiya A, *et al* Successful treatment of positive-sense RNA virus coinfection with autoimmune hepatitis using double filtration plasmapheresis. *BMJ Case Reports CP* 2021;14:e236984.

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ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΑΙΜΑΦΑΙΡΕΣΗΣ

## Προοπτική.....

Successful treatment of positive-sense RNA virus coinfection with autoimmune hepatitis using double filtration plasmapheresis

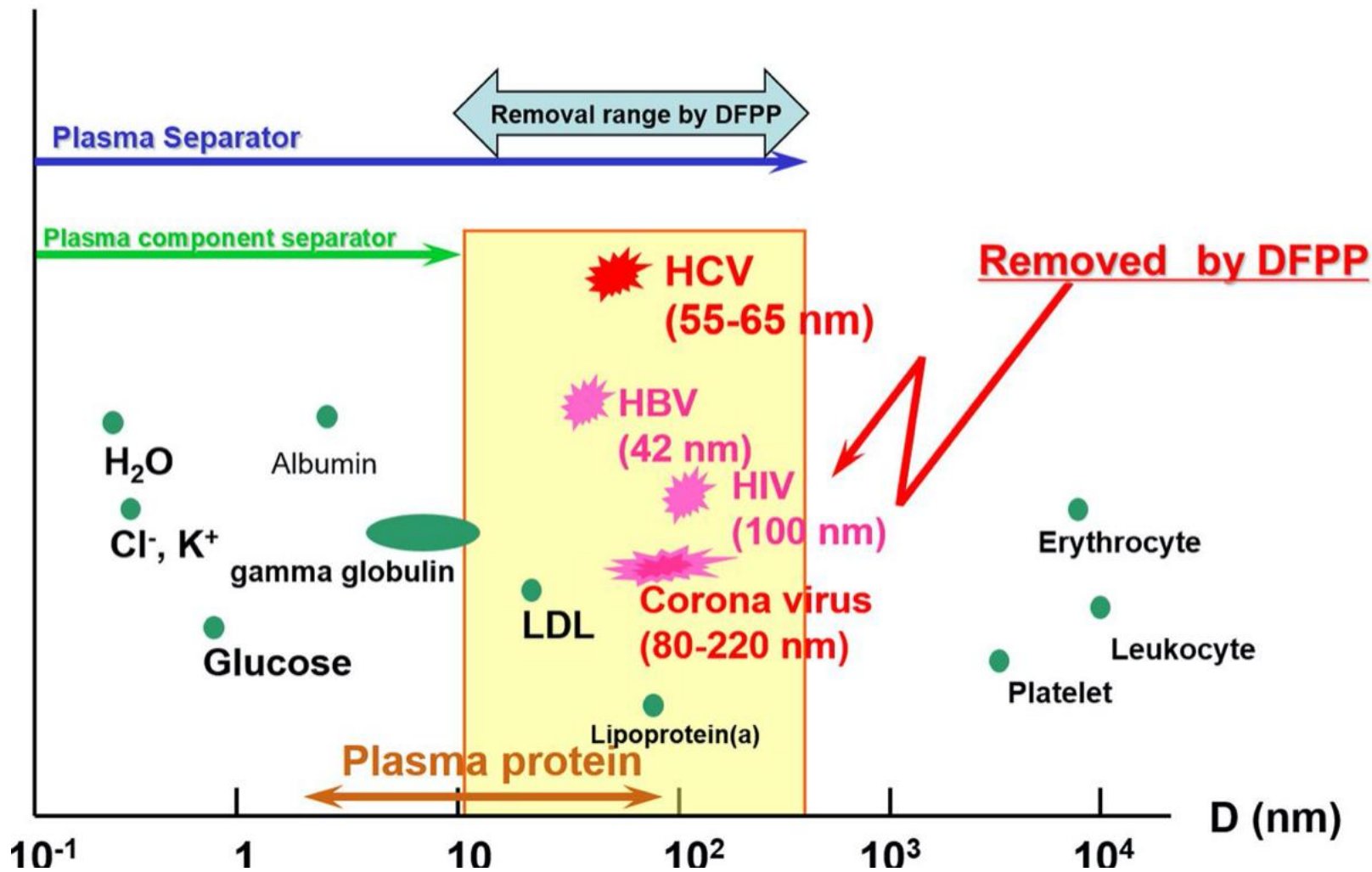
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### Abstract

Double filtration plasmapheresis (DFPP) is an apheretic technique that selectively removes high molecular weight substances using a plasma component filter. DFPP has been used to treat positive-sense RNA virus infections, mainly chronic hepatitis C virus (HCV) infection, because of its ability to directly eliminate viral particles from blood plasma from 2008 to about 2015, before direct-acting antiviral agents was marketed. This effect has been termed virus removal and eradication by DFPP. HCV is a positive-sense RNA virus similar to West Nile virus, dengue virus and the SARS and Middle East respiratory syndrome coronaviruses. SARS-CoV-2 is classified same viral species. These viruses are all classified in Family Flaviviridae which are family of single-stranded plus-stranded RNA viruses. Viral particles are 40–60 nm in diameter, enveloped and spherical in shape. We present a rare case of HCV removal where an RNA virus infection that copresented with virus-associated autoimmune hepatitis was eliminated using DFPP. Our results indicate that DFPP may facilitate prompt viraemia reduction and may have novel treatment applications for SARS-CoV-2, that is, use of therapeutic plasma exchange for fulminant COVID-19.



# Προοπτική ....





ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΑΙΜΑΦΑΙΡΕΣΗΣ

Ευχαριστώ για την προσοχή σας

