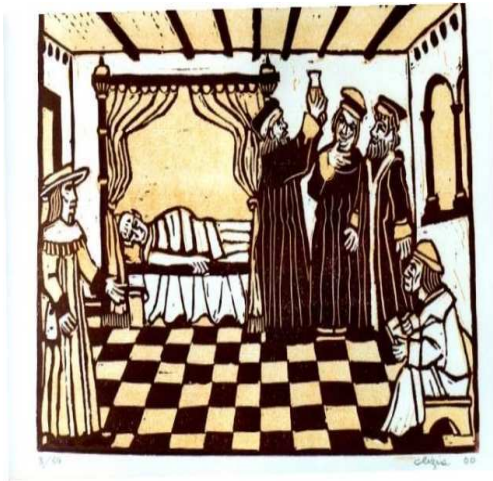

Aferesi terapeutica in Nefrologia: malattie, indicazioni e piani di trattamento

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Coordinamento Interregionale Malattie Rare del Piemonte e della Valle d'Aosta

POSSIBLE MECHANISMS OF APHERESIS IN RENAL DISEASES

Removal of pathological circulating factors, abnormal factors, or excess levels of physiologic factors
- Antibodies: anti-GBM diseases, ANCA-associated diseases, lupus nephritis (anti-DNA), anti-phospholipid diseases
- Immune-complexes: lupus nephritis, cryoglobulinemia
- Dysproteins: macroglobulinemia, myeloma, amyloid-A protein, LDL (FSGS)
- Toxic factors: endotoxin, permeability factors? (MCNS, FSGS)
- Activated lymphocytes: vasculitis, nephrotic syndrome (MCNS, FSGS)

Replacement of deficient plasma factors
- Thrombotic thrombocytopenic purpura: ADAMTS-13

Other effects on the immune system
- Removal of inflammatory mediators: cytokines/chemokines, cannabinoids
- Improvement of reticuloendothelial system function
- Effects of immune regulation

APPLICATION OF APHERESIS TECHNIQUES FOR RENAL DISEASES

Procedure	Ligands or materials	Removed or adsorbed factors
Plasma exchange	Replacement of plasma[a]	Autoantibodies, CIC, dysproteins
Double filtration	Plasma fractionator	CIC, autoantibodies, dysproteins
Cryofiltration	Plasma fractionator	Cryoproteins
Plasma adsorption	Phenylalanine or Tryptophan	Anti-DNA, CIC
	Dextran sulfate	Anti-DNA, CIC, lupus anticoagulants, LDL
	Protein or Tryptophan	IgG, CIC, permeability factors (?)
	Anti-IgG Fc	IgG, CIC, permeability factors (?)
Blood adsorption	Polymyxin B (dextran sulfate)	Endotoxin, cytokines
Cytapheresis		
LCAP[b]	Lymphocyte separators	Lymphocytes, activated platelets
GCAP[c]	Granulocyte separators	Granulocytes

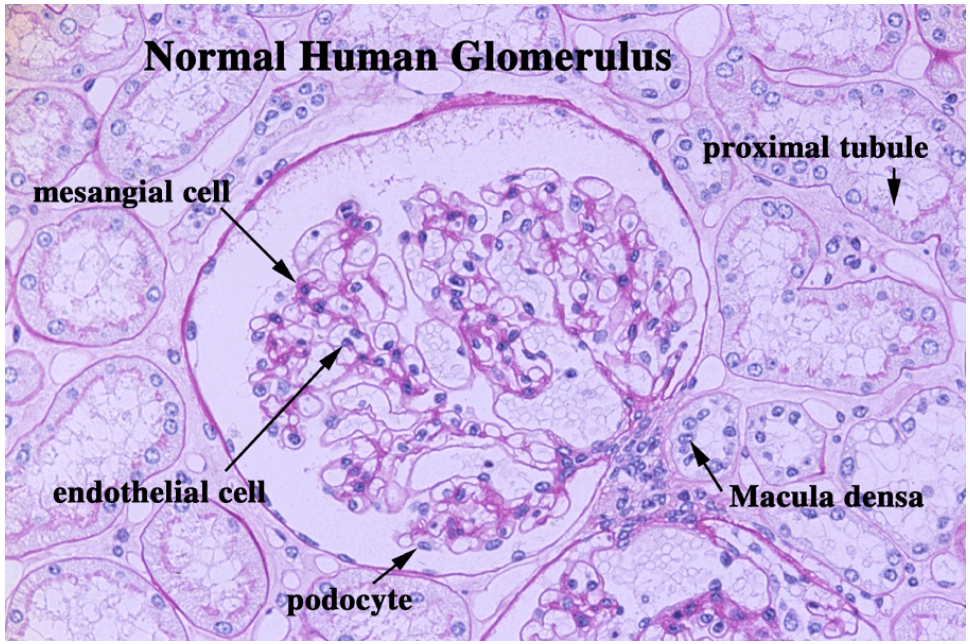
Yokoyama H, Clin Exp Nephrol 2007

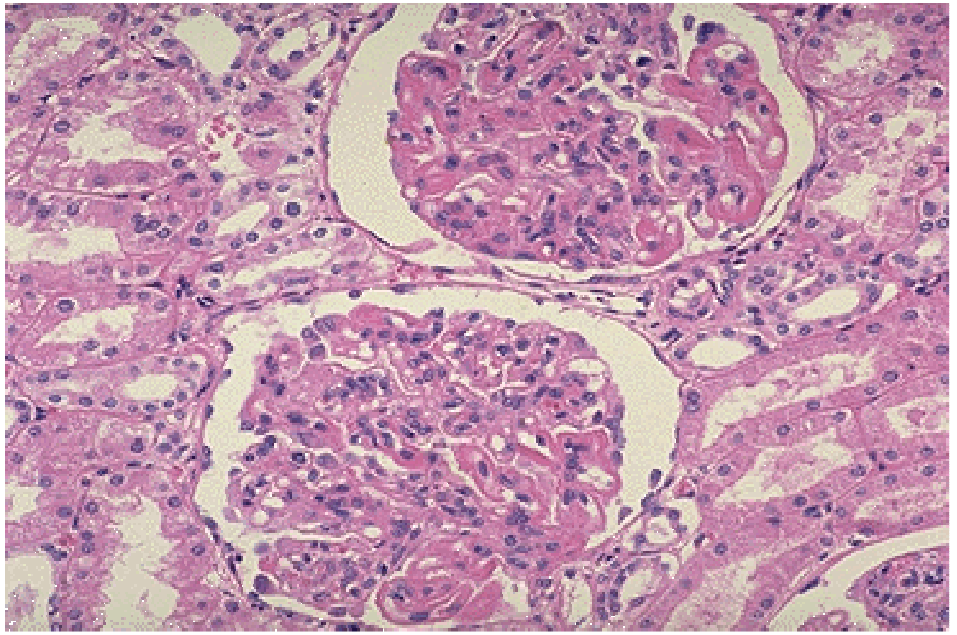
INDICATIONS FOR PLASMAPHERESIS IN RENAL DISEASES

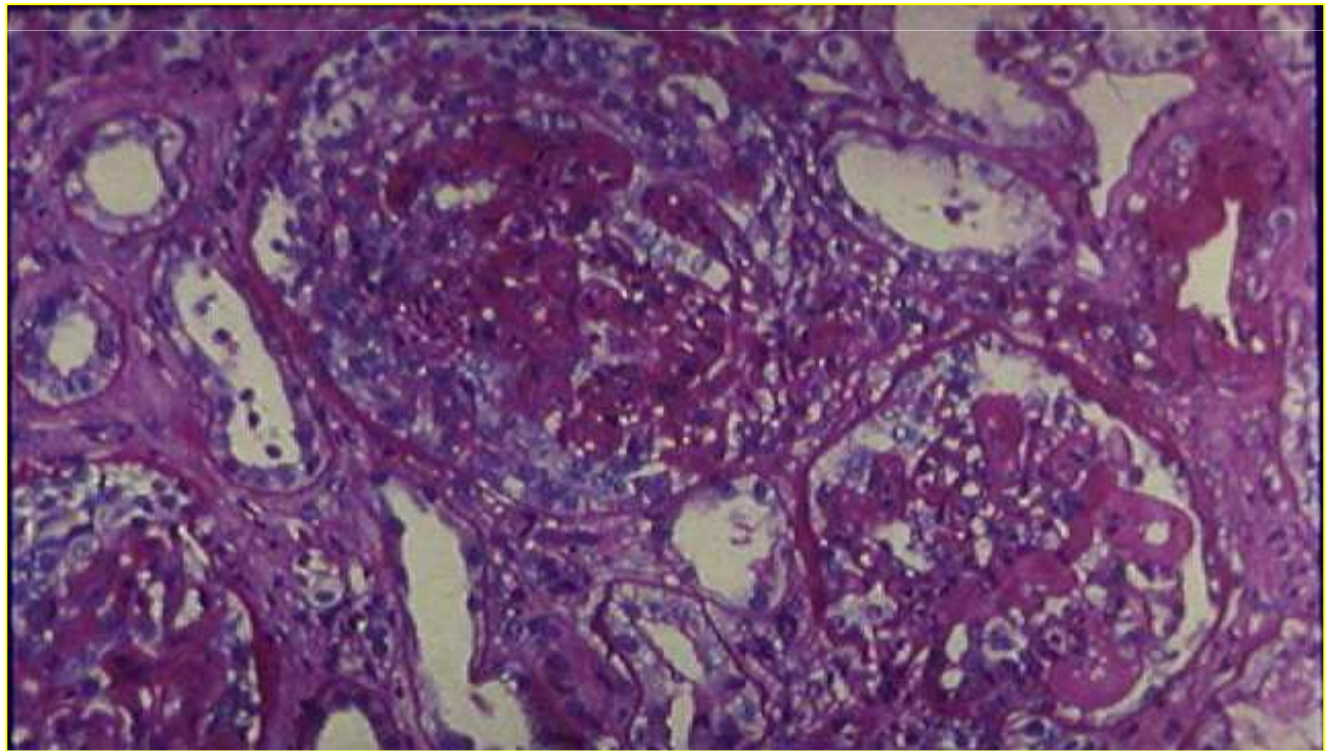
Disease	Rating
Anti-GBM disease	1
Rapidly progressive glomerulonephritis	2
Thrombotic thrombocytopenic purpura	1
Hemolytic uremic syndrome	3–4
Cryoglobulinemia	1
Multiple myeloma cast nephropathy	3
Hyperviscosity syndrome (Waldenström's macroglobulinemia)	1
Removal of cytotoxic antibodies in transplant candidate	2
Renal allograft rejection	2
Focal segmental glomerulosclerosis (recurrence after transplantation)	2
Rheumatoid arthritis/rheumatoid vasculitis	2
Antiphospholipid antibody syndrome	2
Systemic lupus erythematosis	4
Scleroderma	4

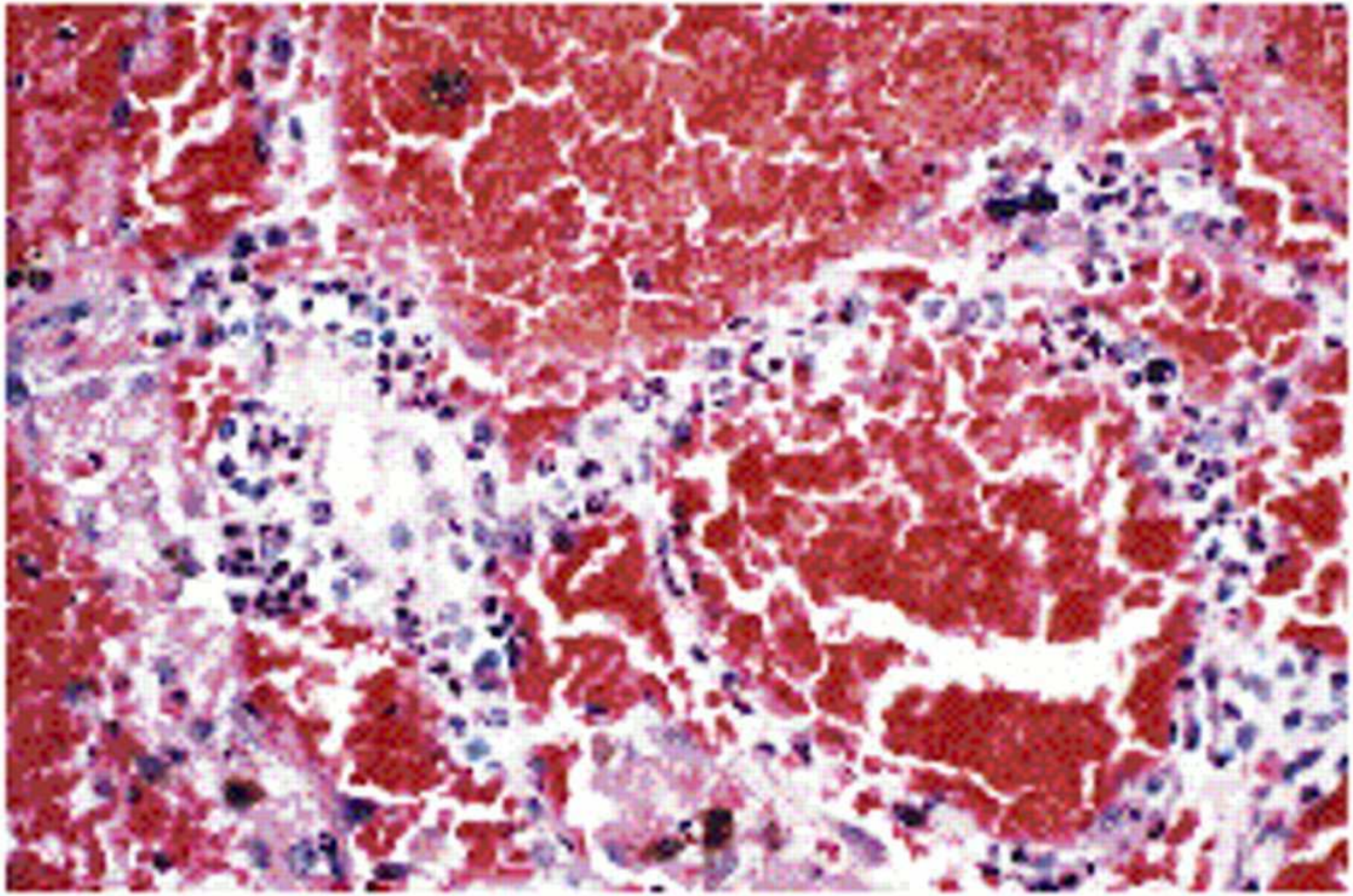
1standard therapy
2 conventional therapy tried first
3 inadequately tested
4 no value in controlled trials

Szczepiorkowski ZM, J Clin Apher 2007


Normal Human Glomerulus
proximal tubule
mesangial cell
endothelial cell
Macula densa
podocyte

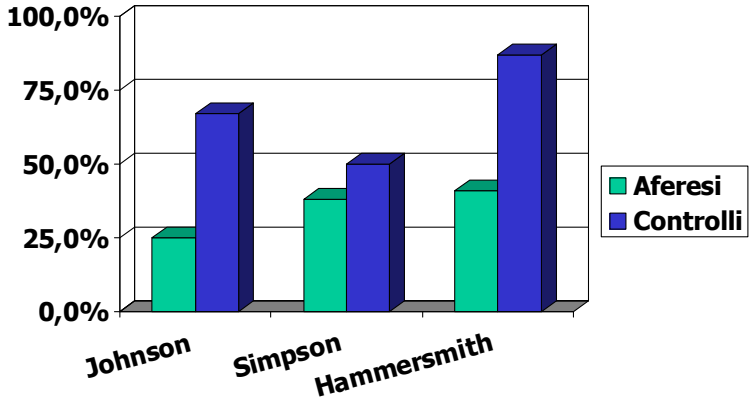




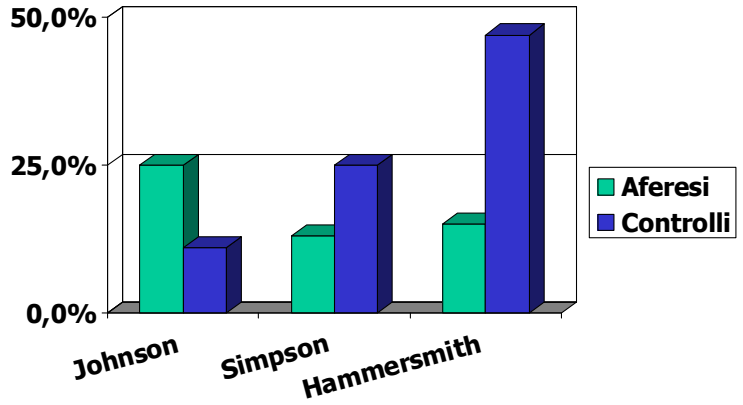


Plasmaferesi nel trattamento della malattia da Ab anti-MB

mortalità rene



mortalità paziente



Hammersmith long-term (2001):
1-year pt/renal survival:
100 & 95% if < 500 micromol sCr
83 & 82 if > 500, but HD-independent
65 & 8 if HD-dependent

ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE (GOODPASTURE'S SYNDROME)

Incidence: 1 per 100,000/year

Procedure	Recommendation	Category
TPE	Grade 1A	I** (dialysis independent)
TPE	Grade 1B	I** [diffuse alveolar hemorrhage (DAH)]
TPE	Grade 1A	IV** (dialysis dependent; no DAH)

# of reported patients*: >300

RCT	CT	CS	CR	Type of evidence
1 (17)	0	17 (430)	17	Type I

**See technical notes

TECHNICAL NOTES

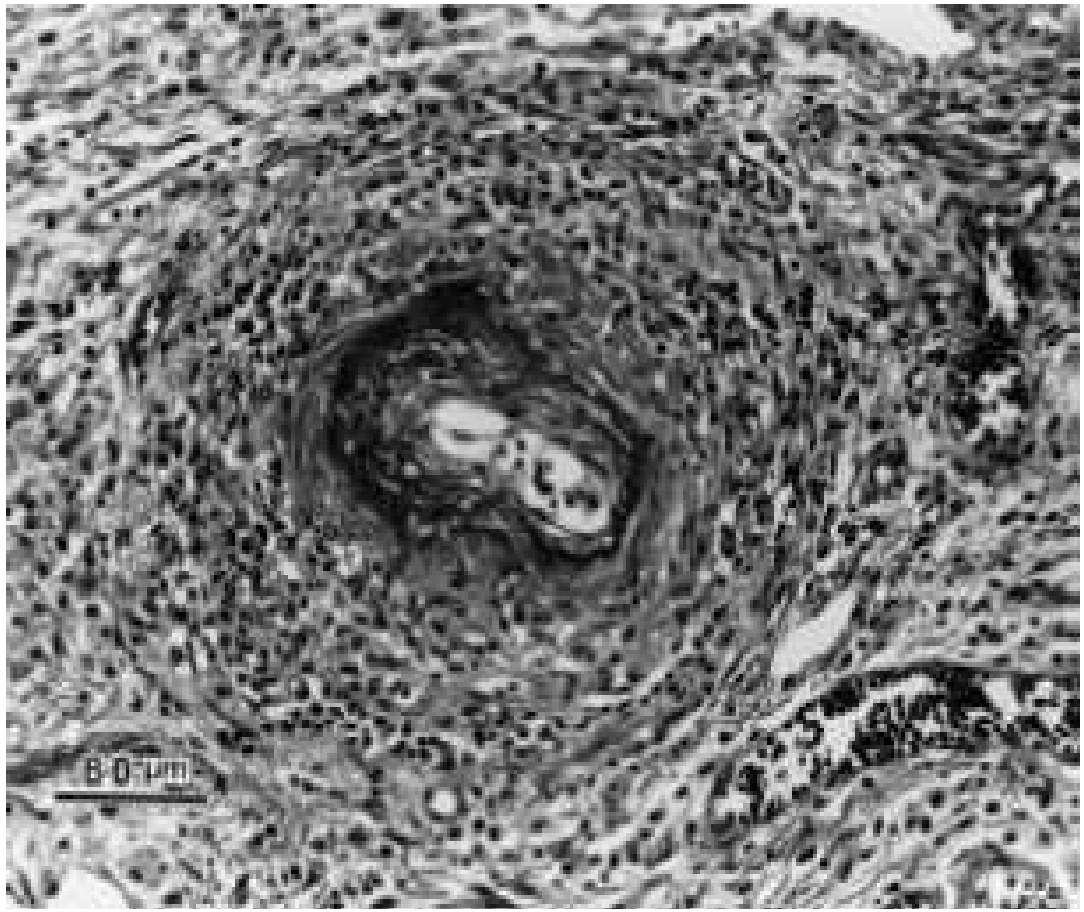
Volume treated: 1 to 1.5 TPV

Frequency: daily or every other day

Replacement fluid: albumin, plasma

Szczepiorkowski ZM, J Clin Apher 2010

Necrosi fibrinoide ed infiltrato infiammatorio arteriolare



- colpite segmentariamente biforcazioni e ramificazioni
- PMN (proliferazione intimale e degenerazione della parete) >mononucleati (cronicizzazione)
- necrosi fibrinoide > trombosi > infarto > talora emorragia

Classificazione delle vasculiti

VASI DI GROSSO CALIBRO

- **Arterite a cellule giganti**
- **Arterite di Takayasu**

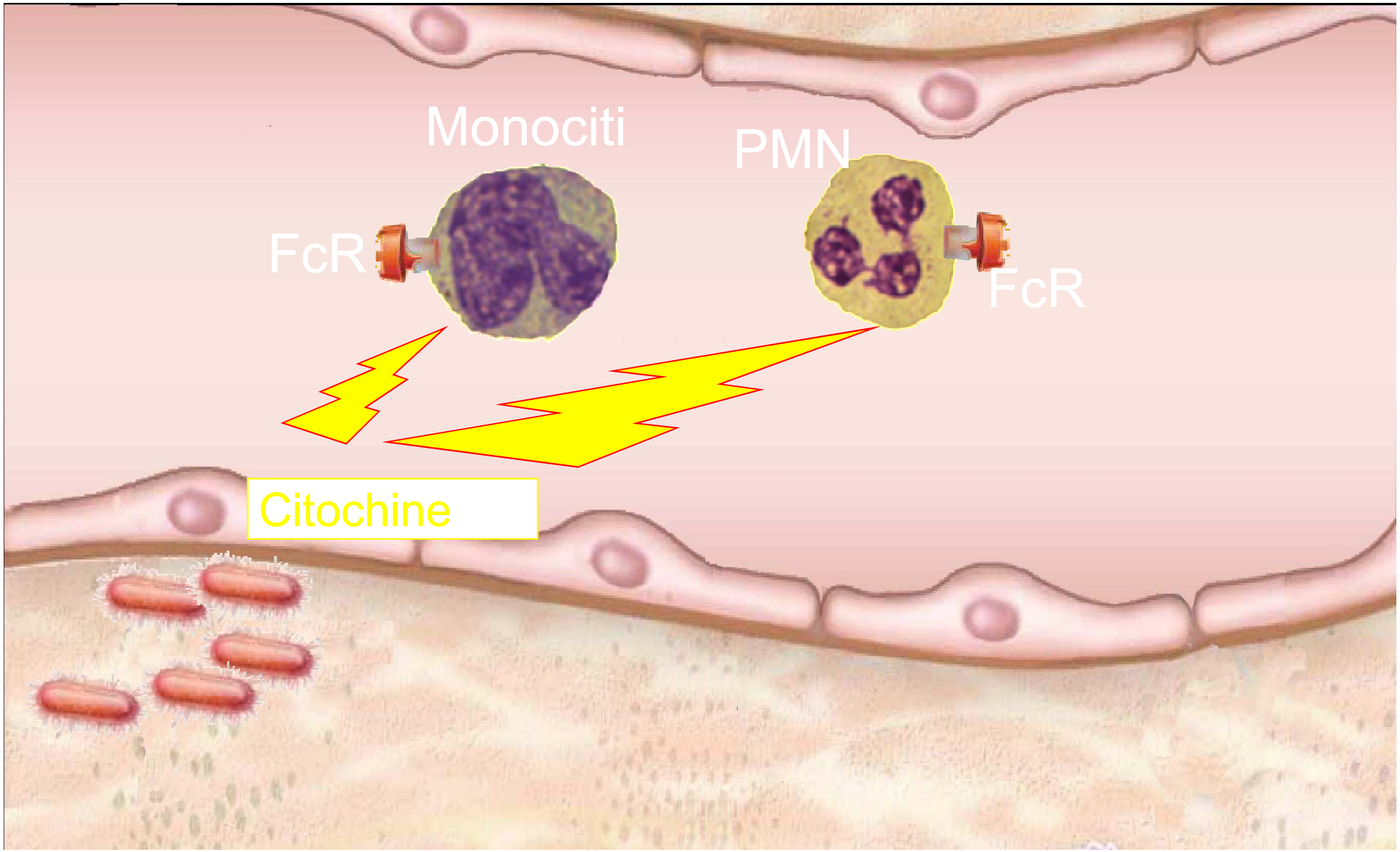
VASI DI MEDIO CALIBRO

- **Panarterite nodosa**
- **Malattia di Kawasaki**

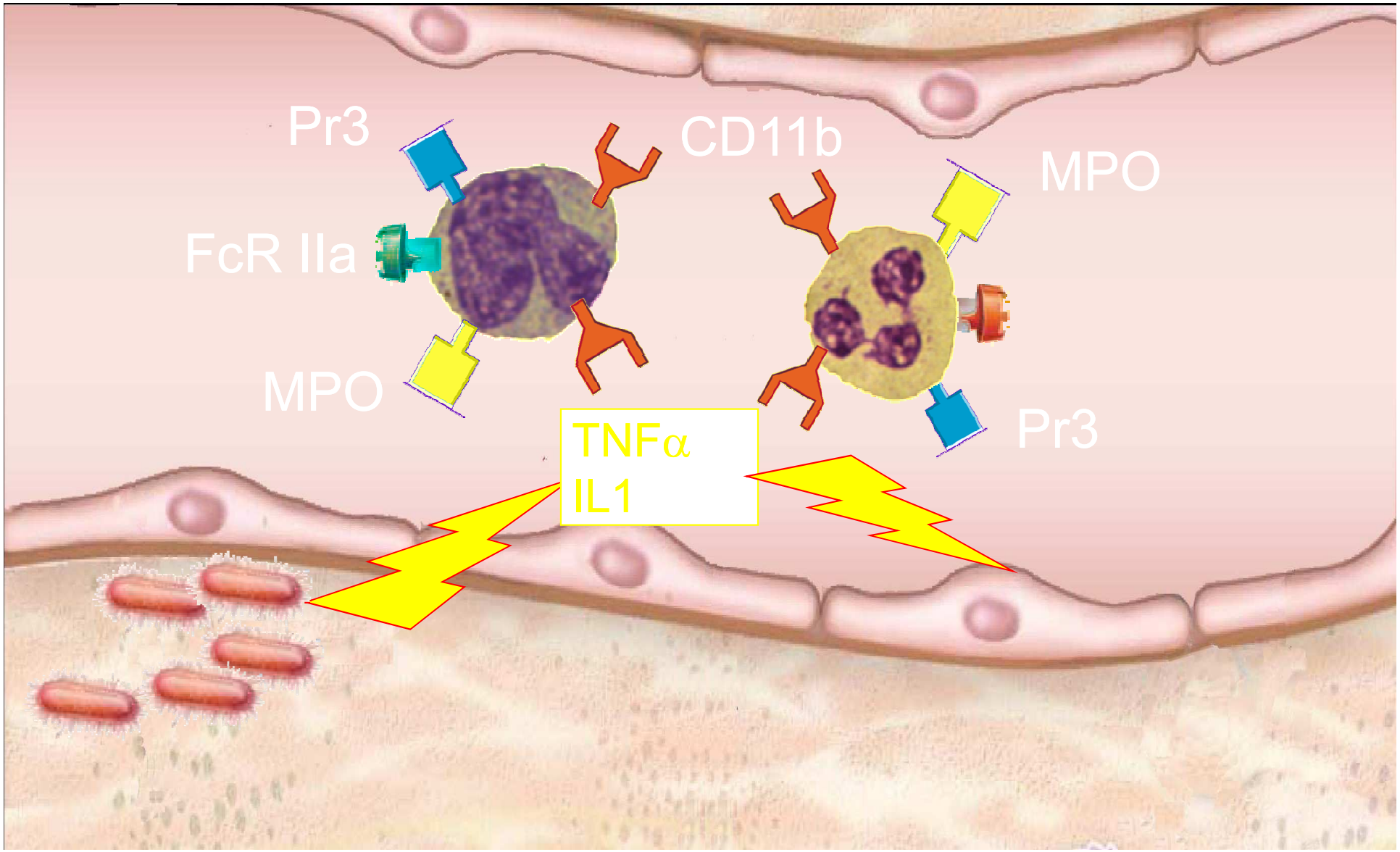
VASI DI PICCOLO CALIBRO

- **Granulomatosi di Wegener**
- **Sindrome di Churg-Strauss**
- **Micropoliangioite**
- **Porpora di Schonlein Henoch**
- **Vasculite crioglobulinemica**
- **Angioite cutanea leucocitoclastica**

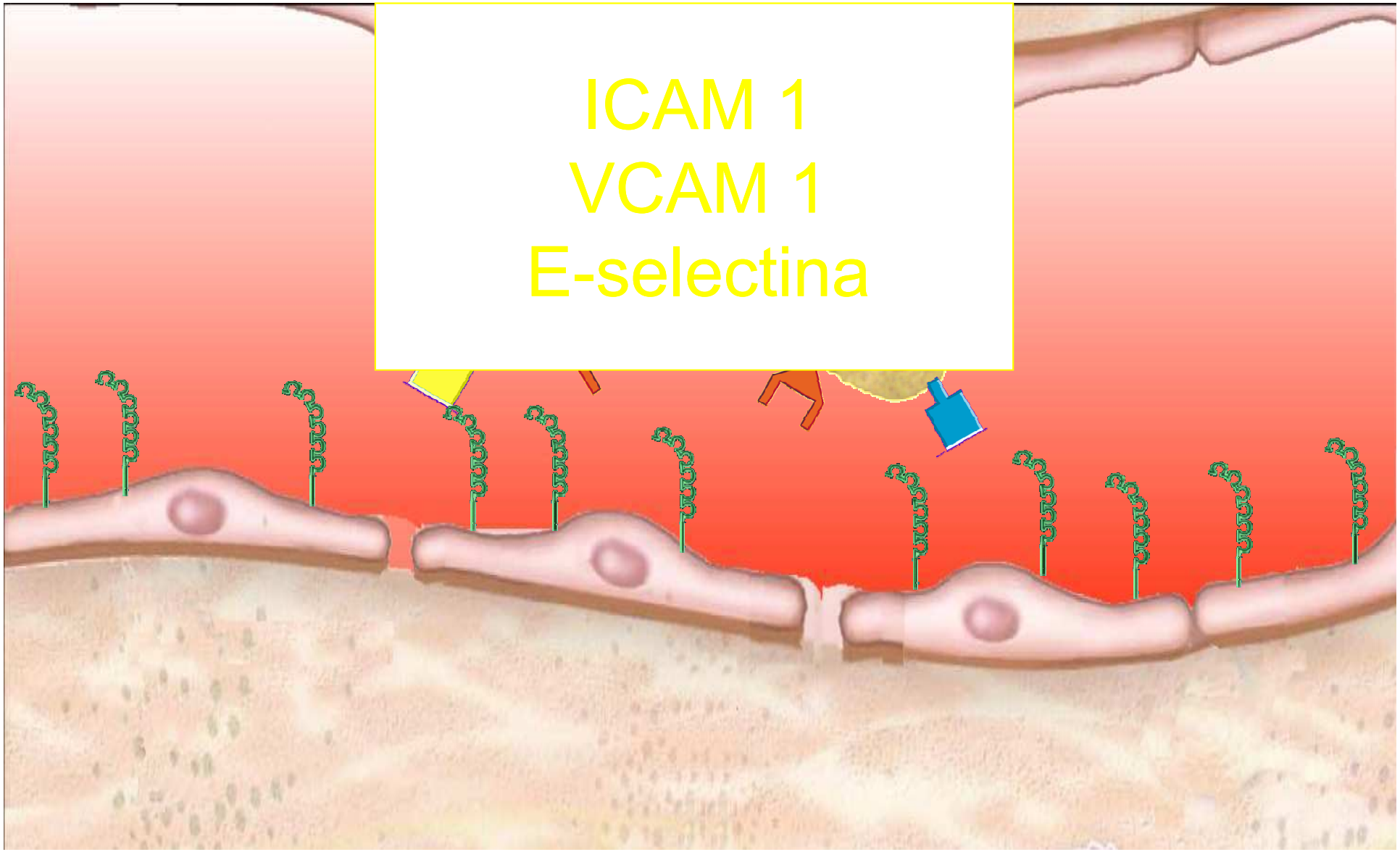
Patogenesi: cellule circolanti quiescenti



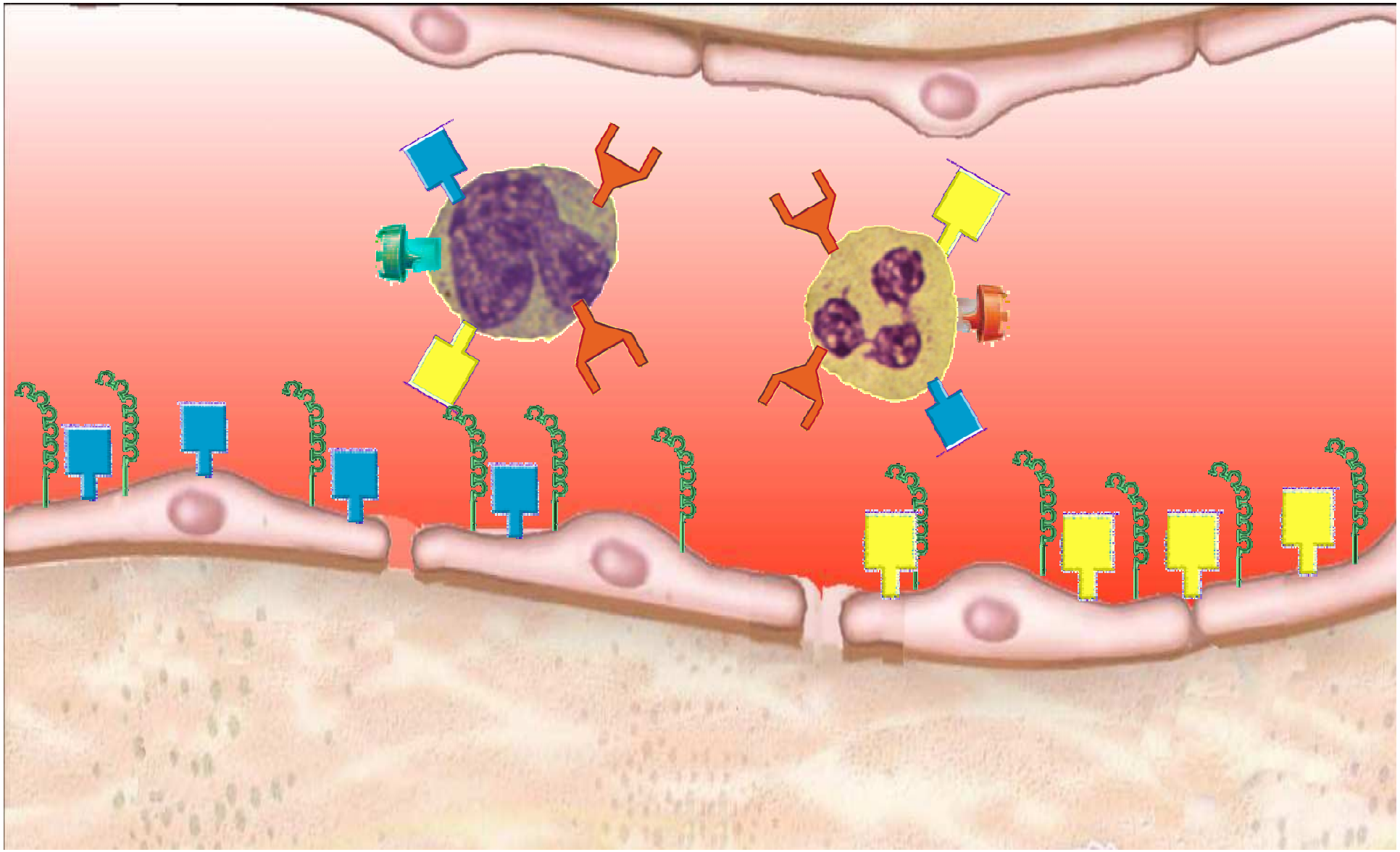
Patogenesi: cellule circolanti primed



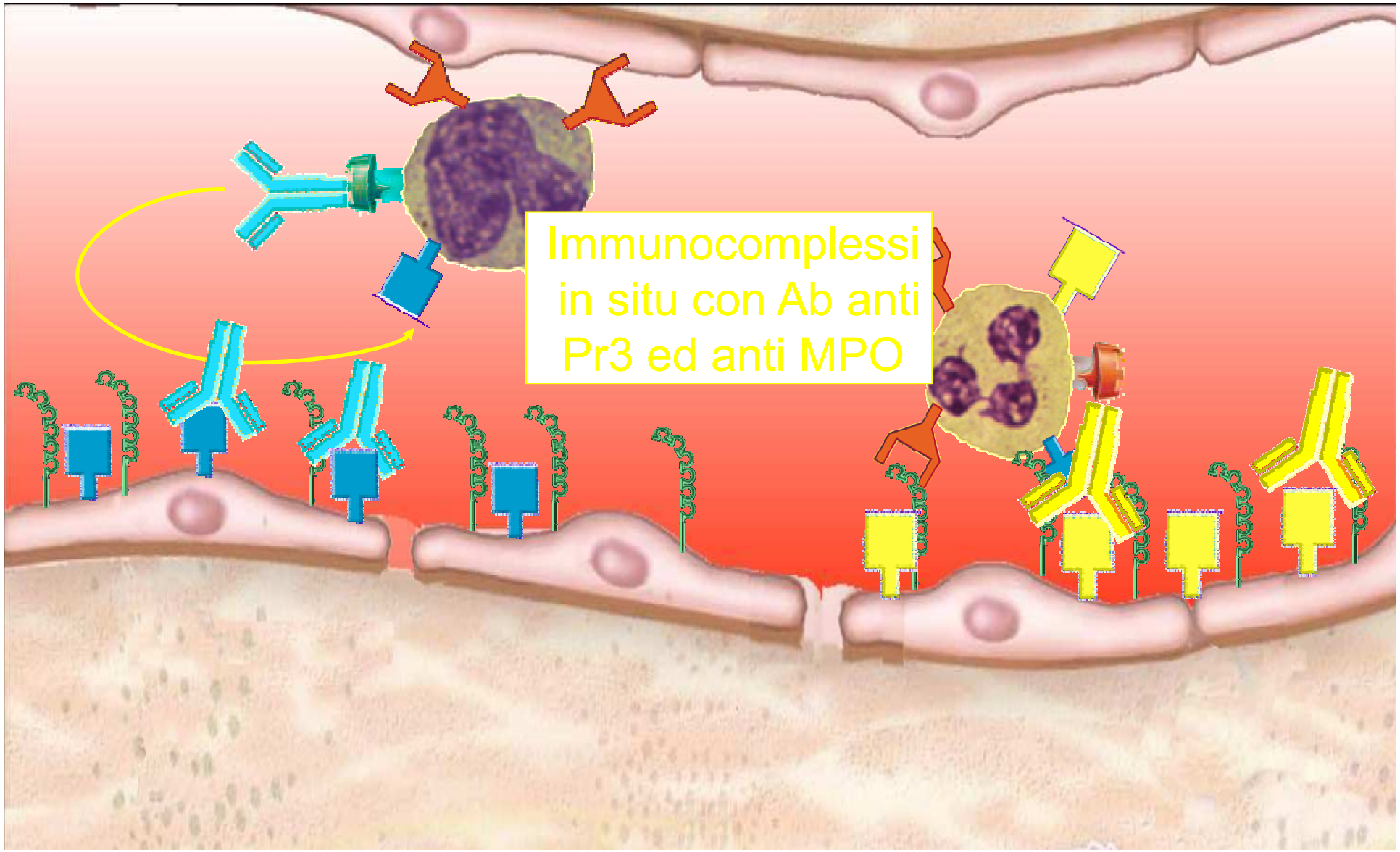
Patogenesi: attivazione endotelio



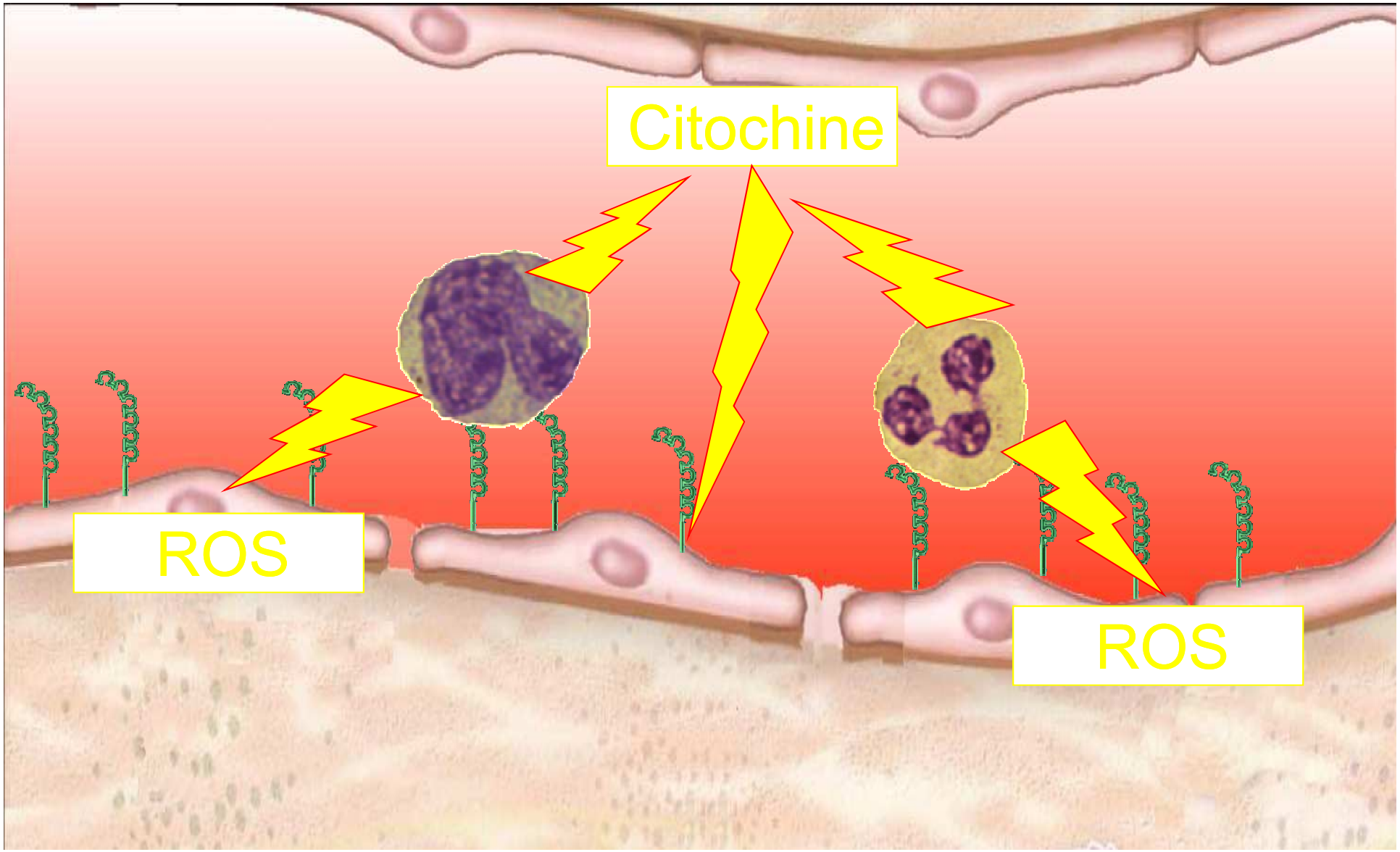
Patogenesi: legame Pr3-ANCA



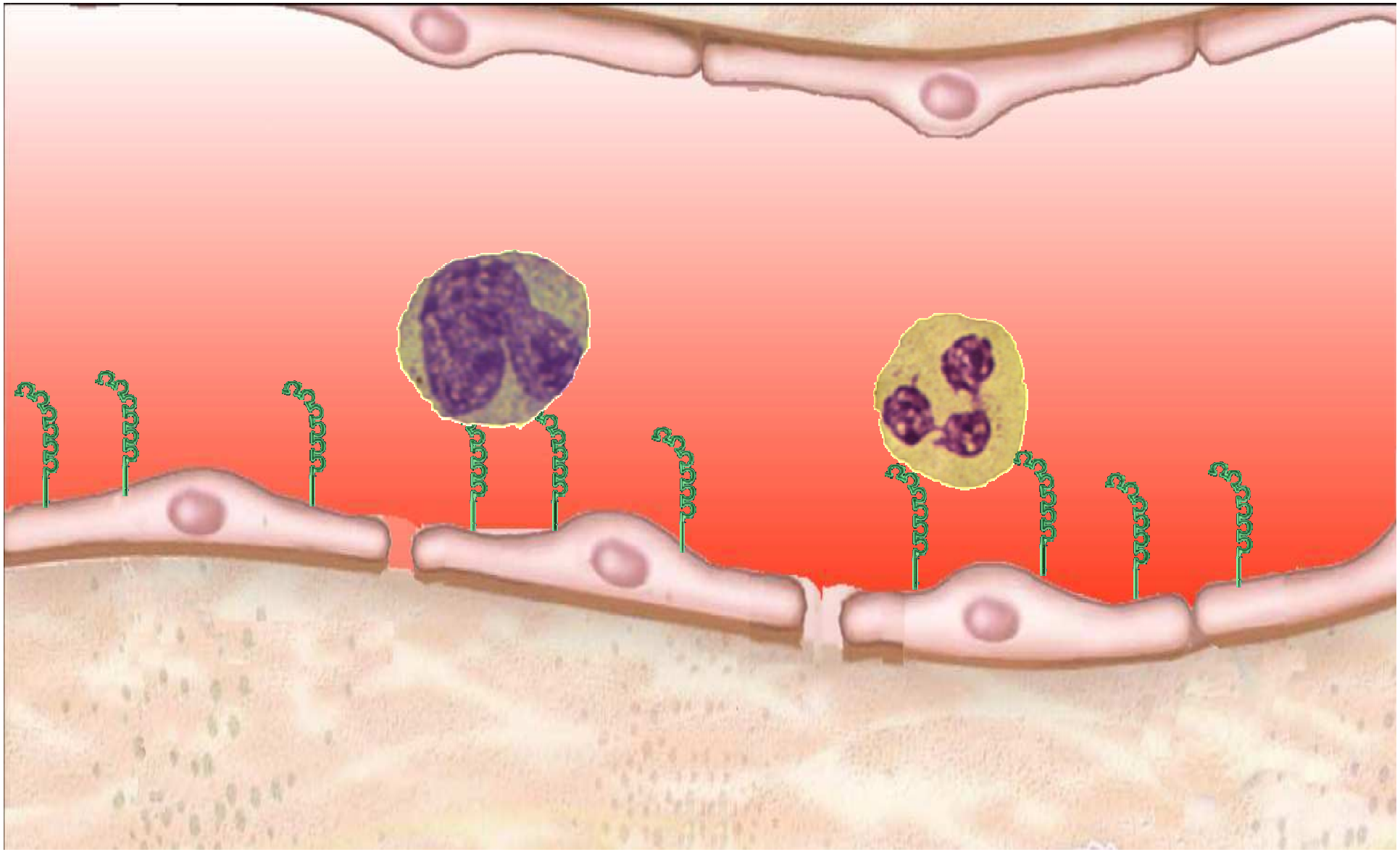
Patogenesi: azione ANCA



Patogenesi: lesione endotelio



Patogenesi: migrazione leucocitaria



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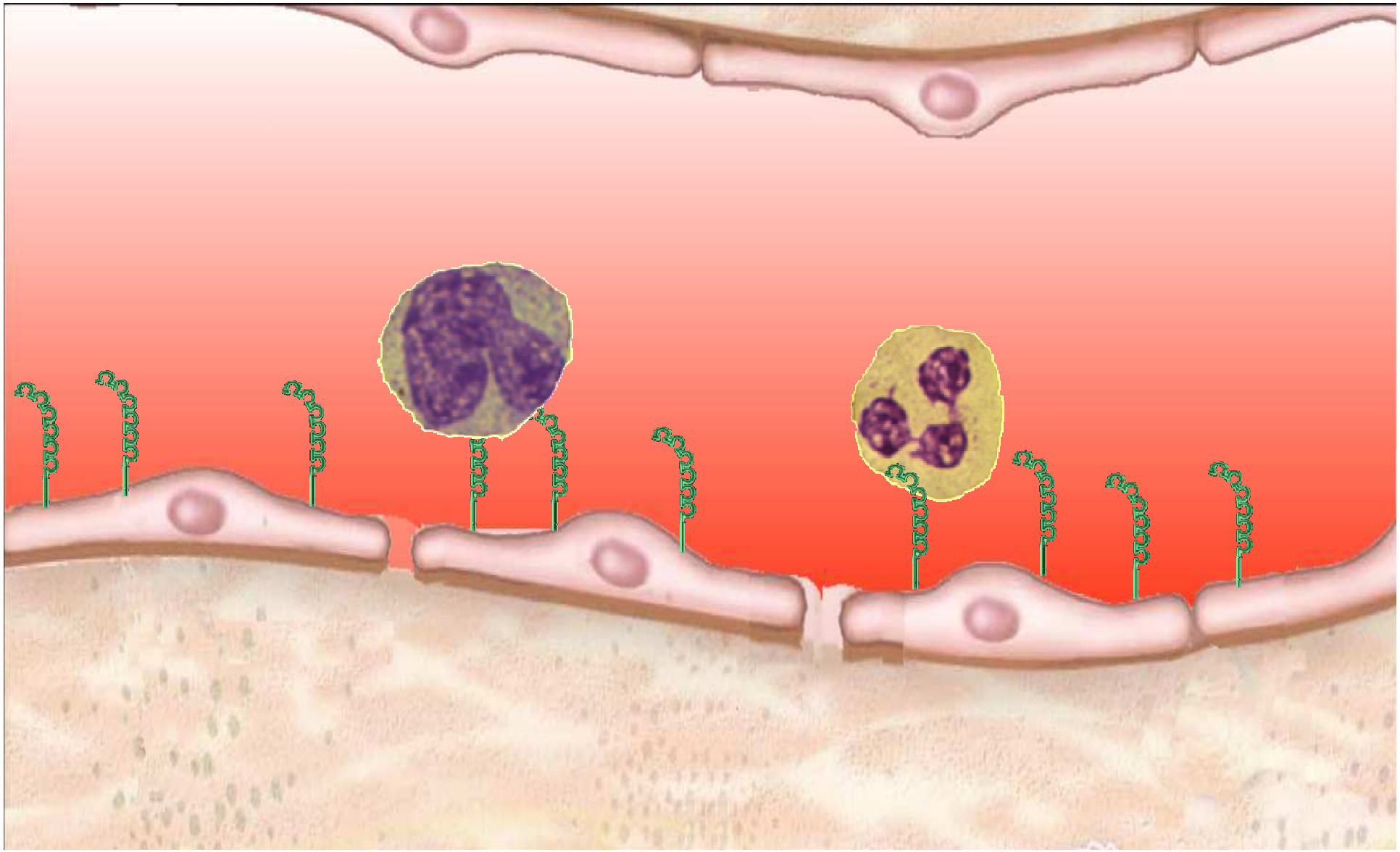

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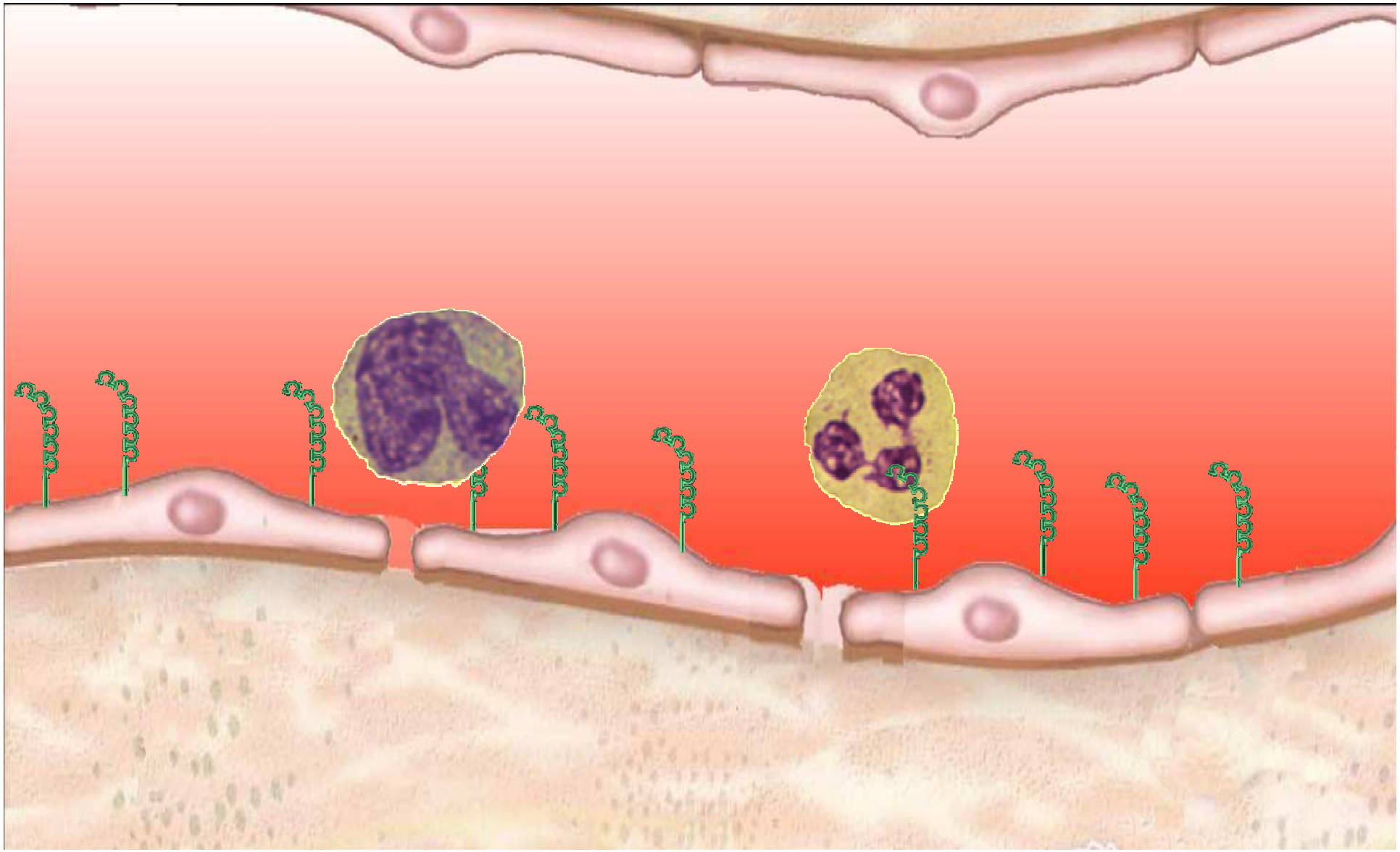

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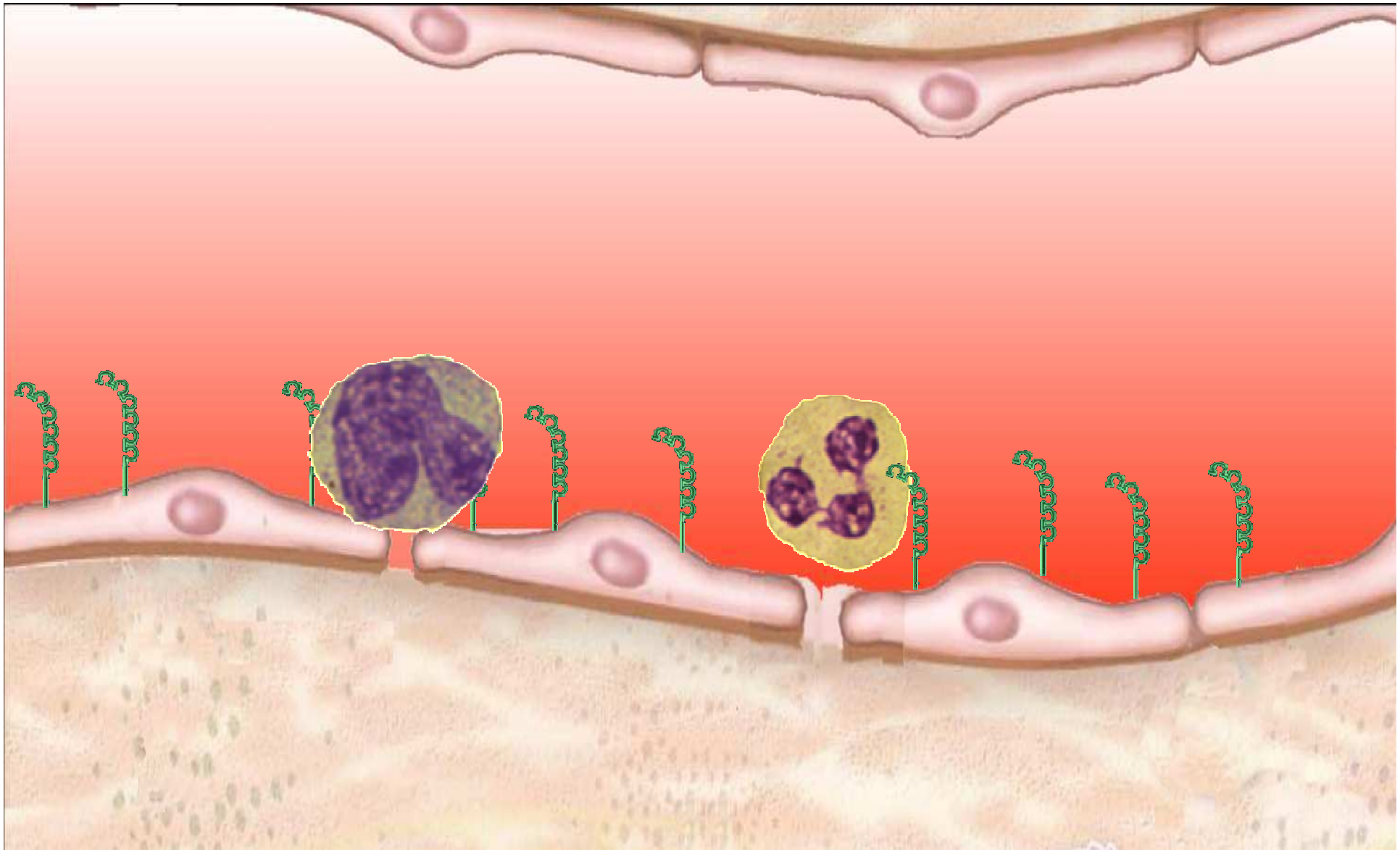

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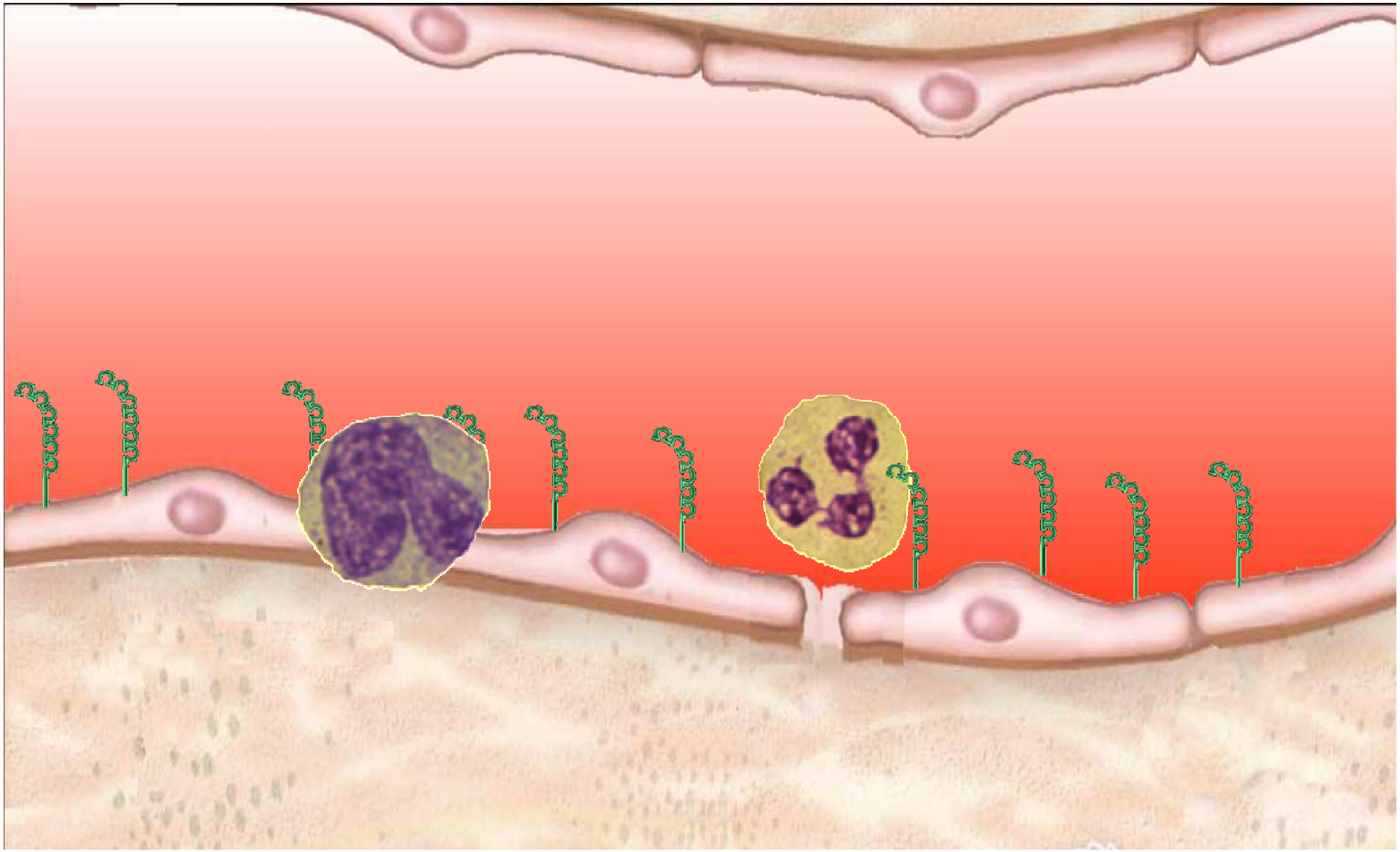

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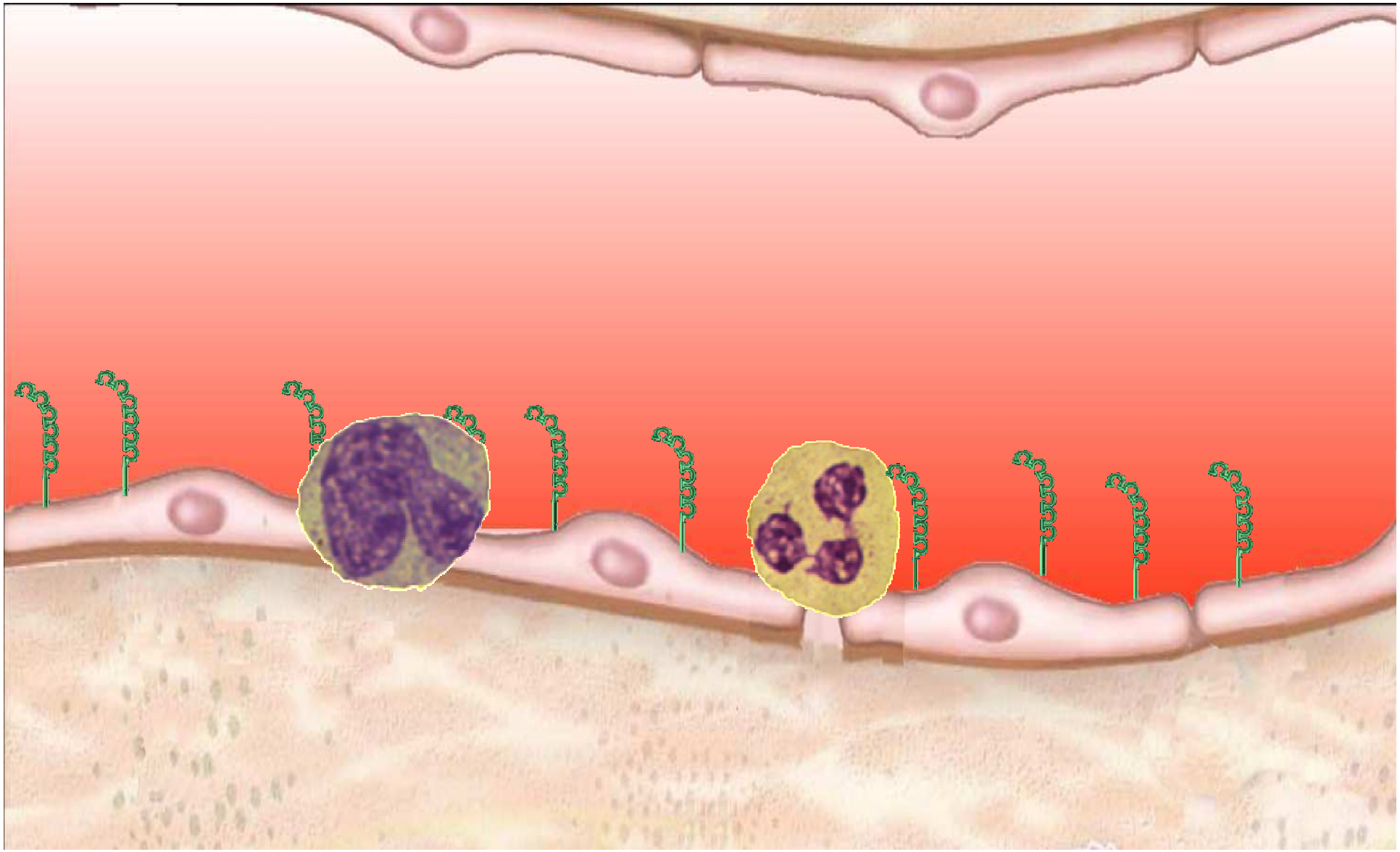
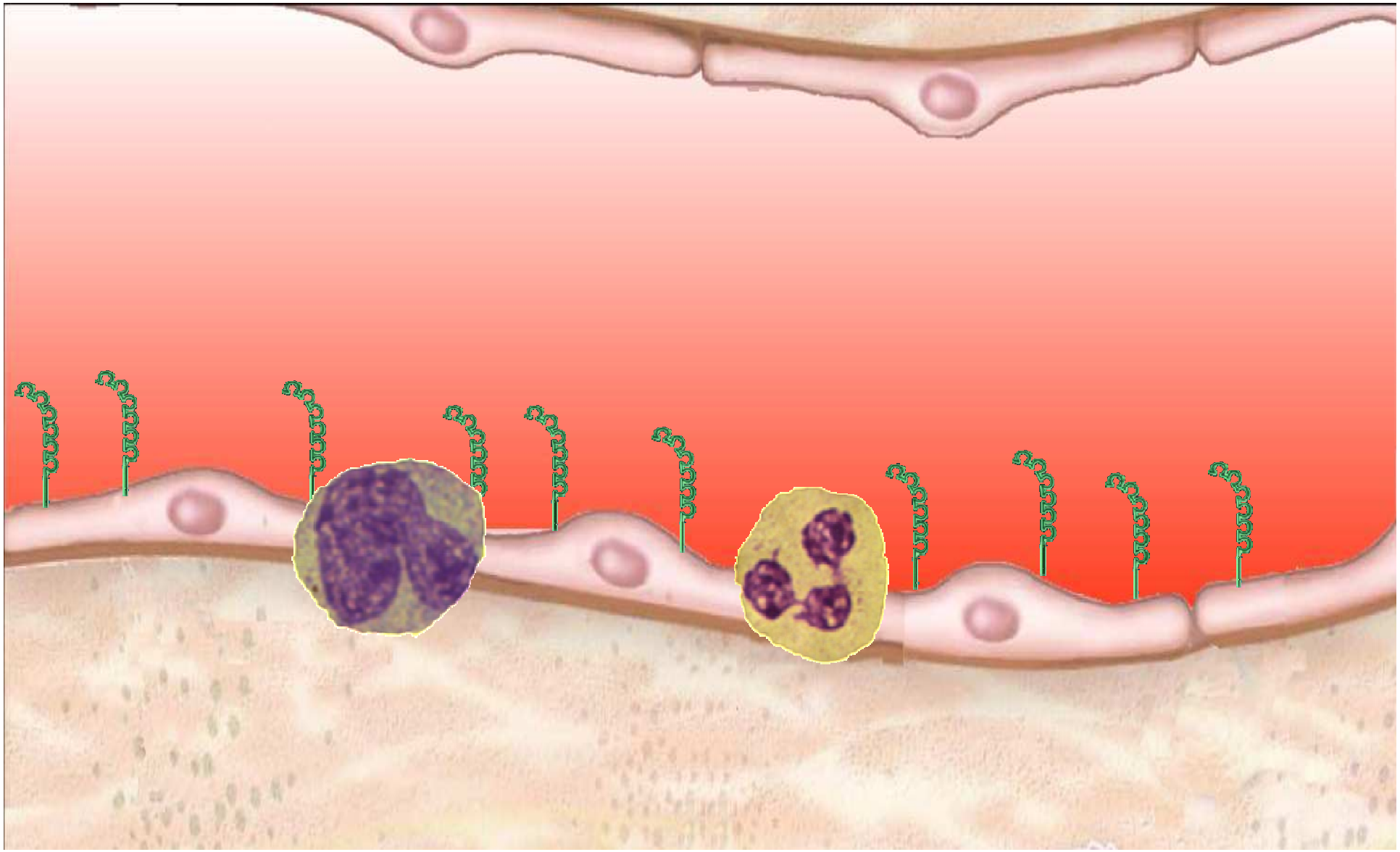
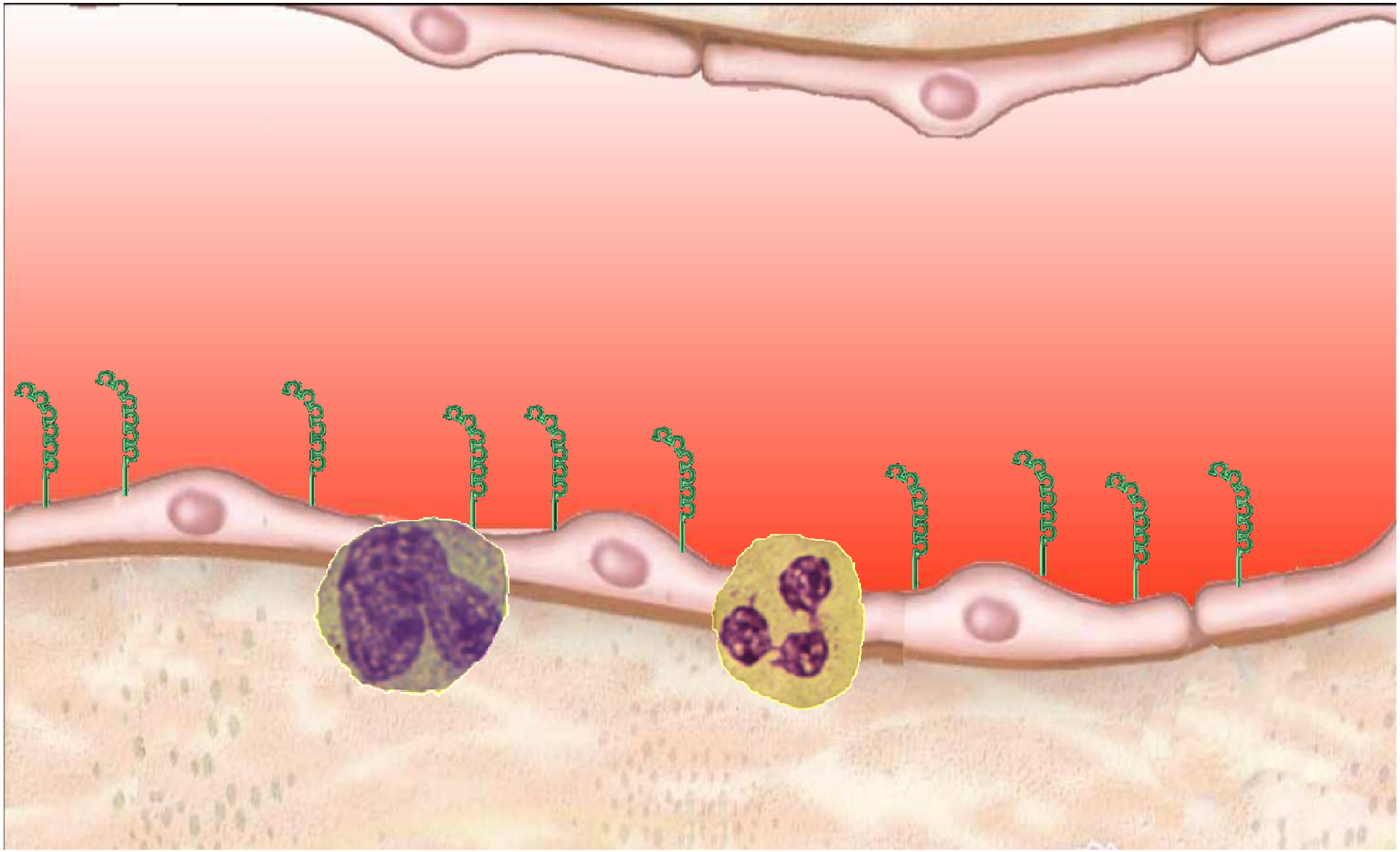


Patogenesi: migrazione leucocitaria



Patogenesi: migrazione leucocitaria



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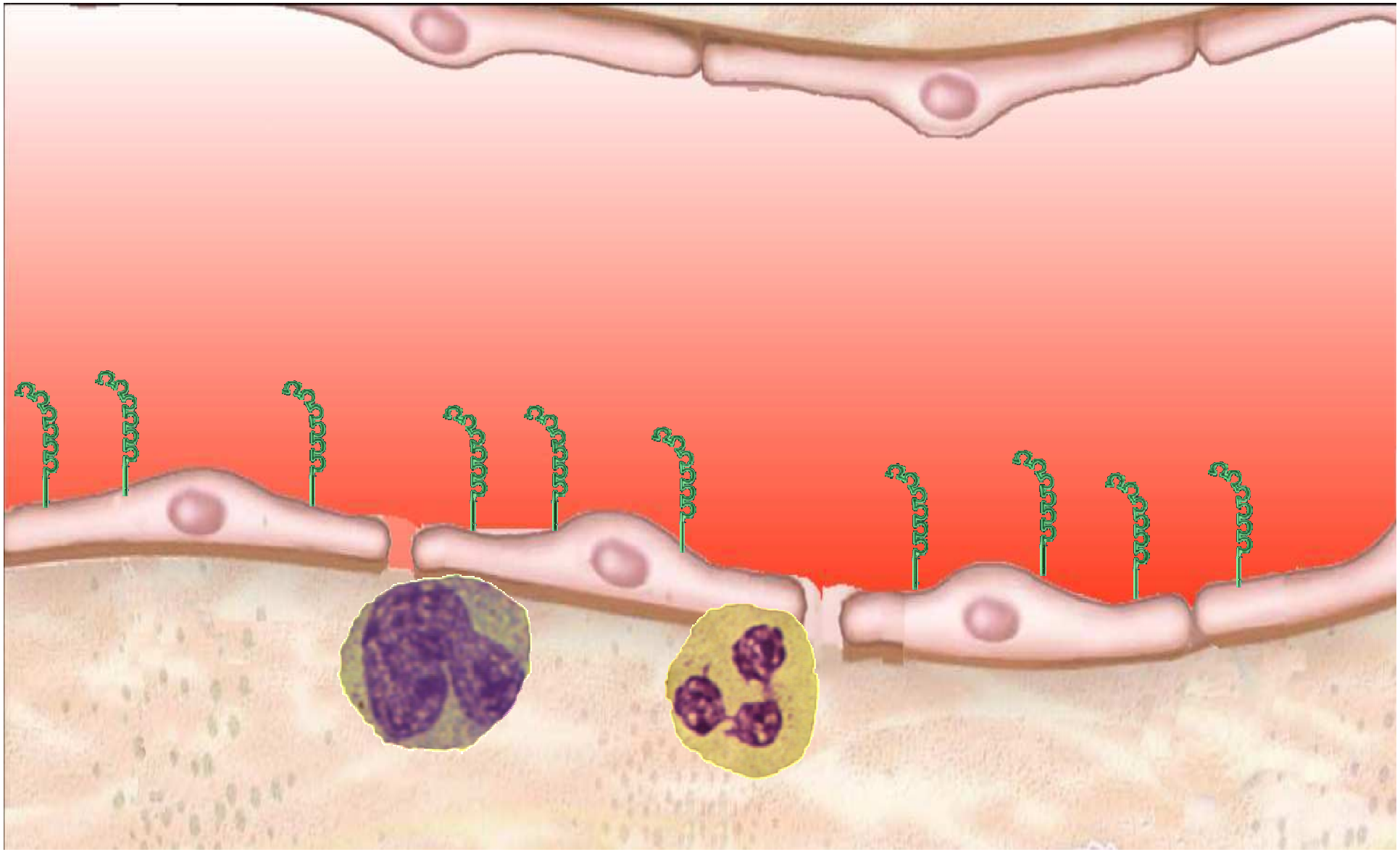
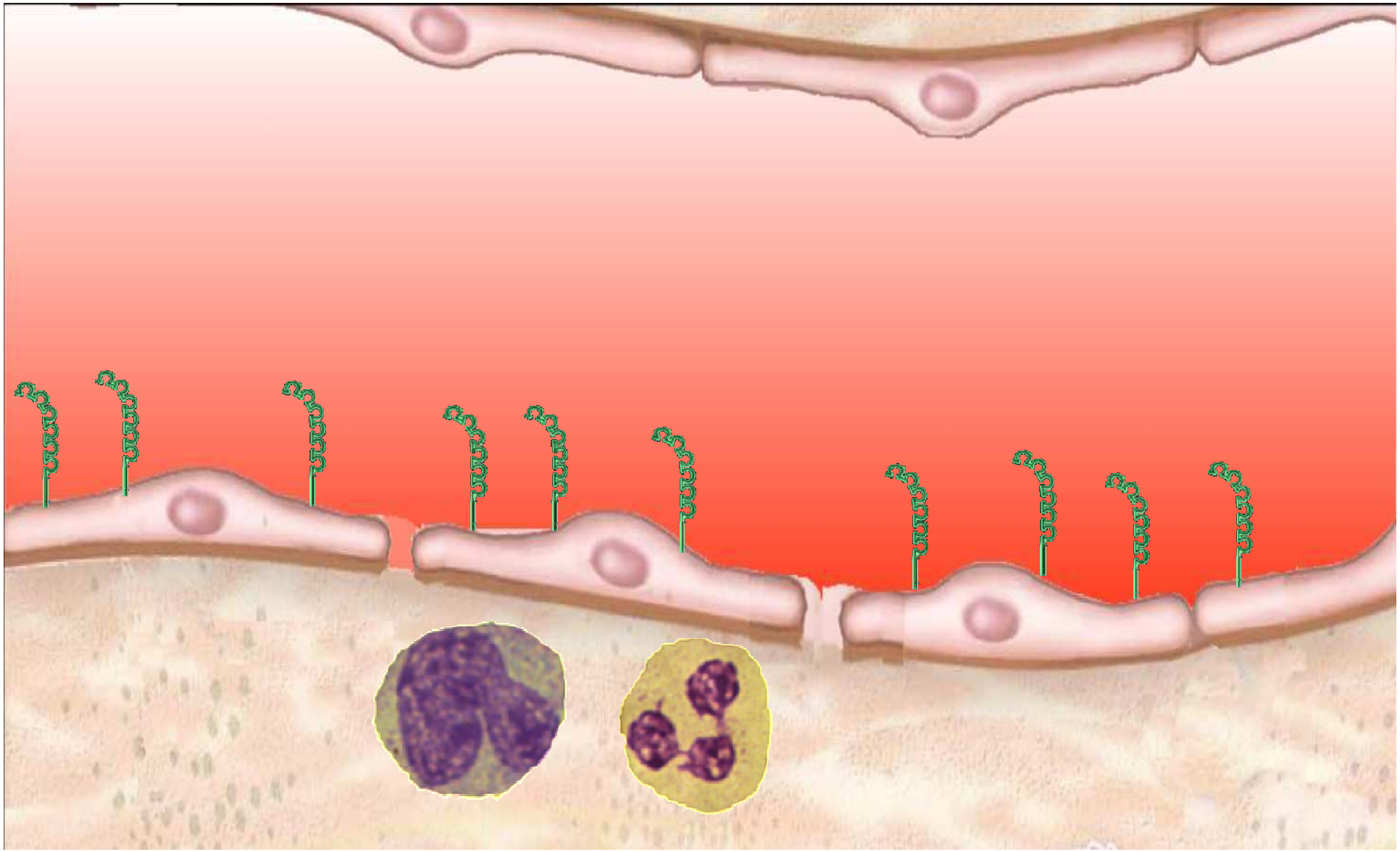
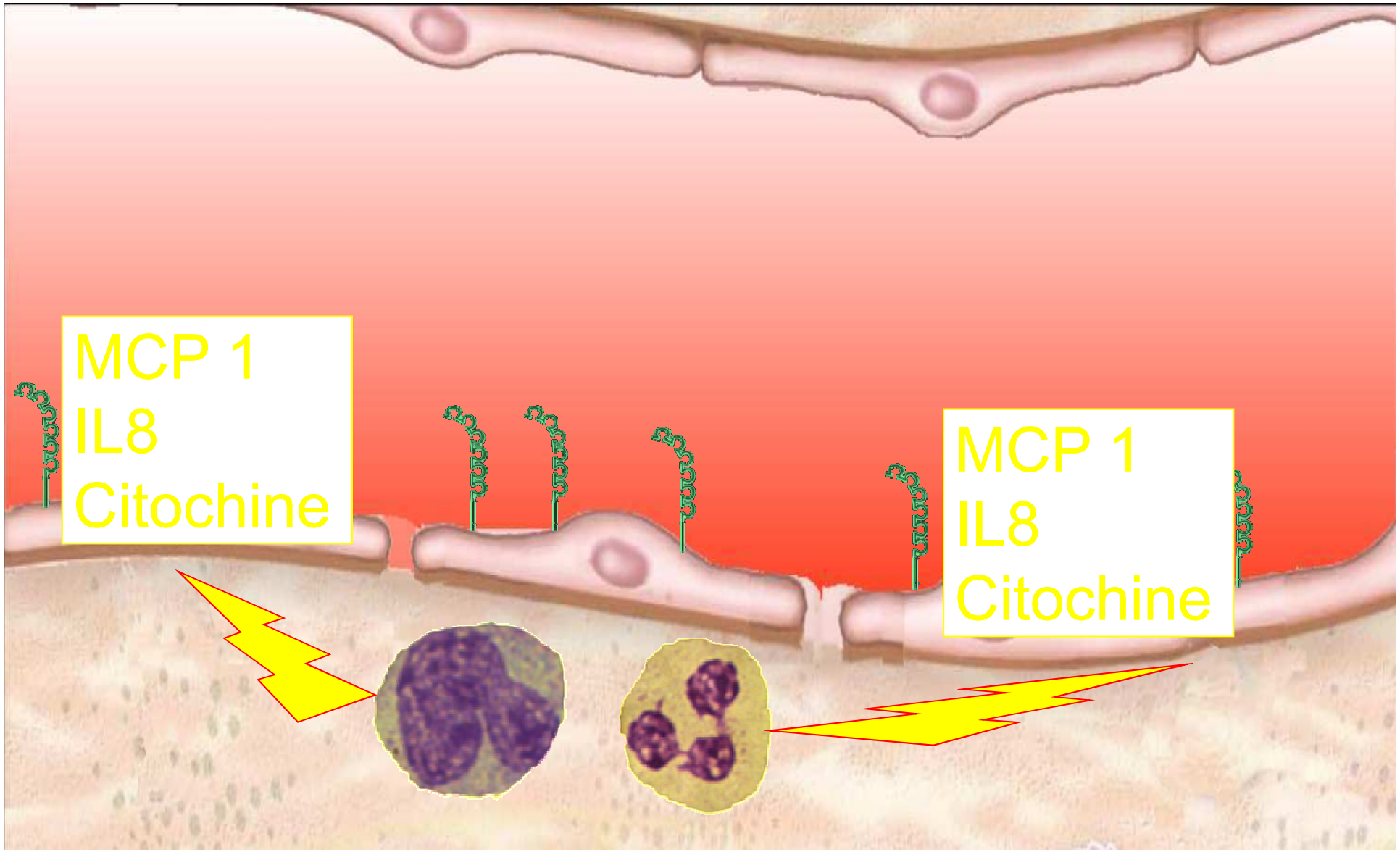
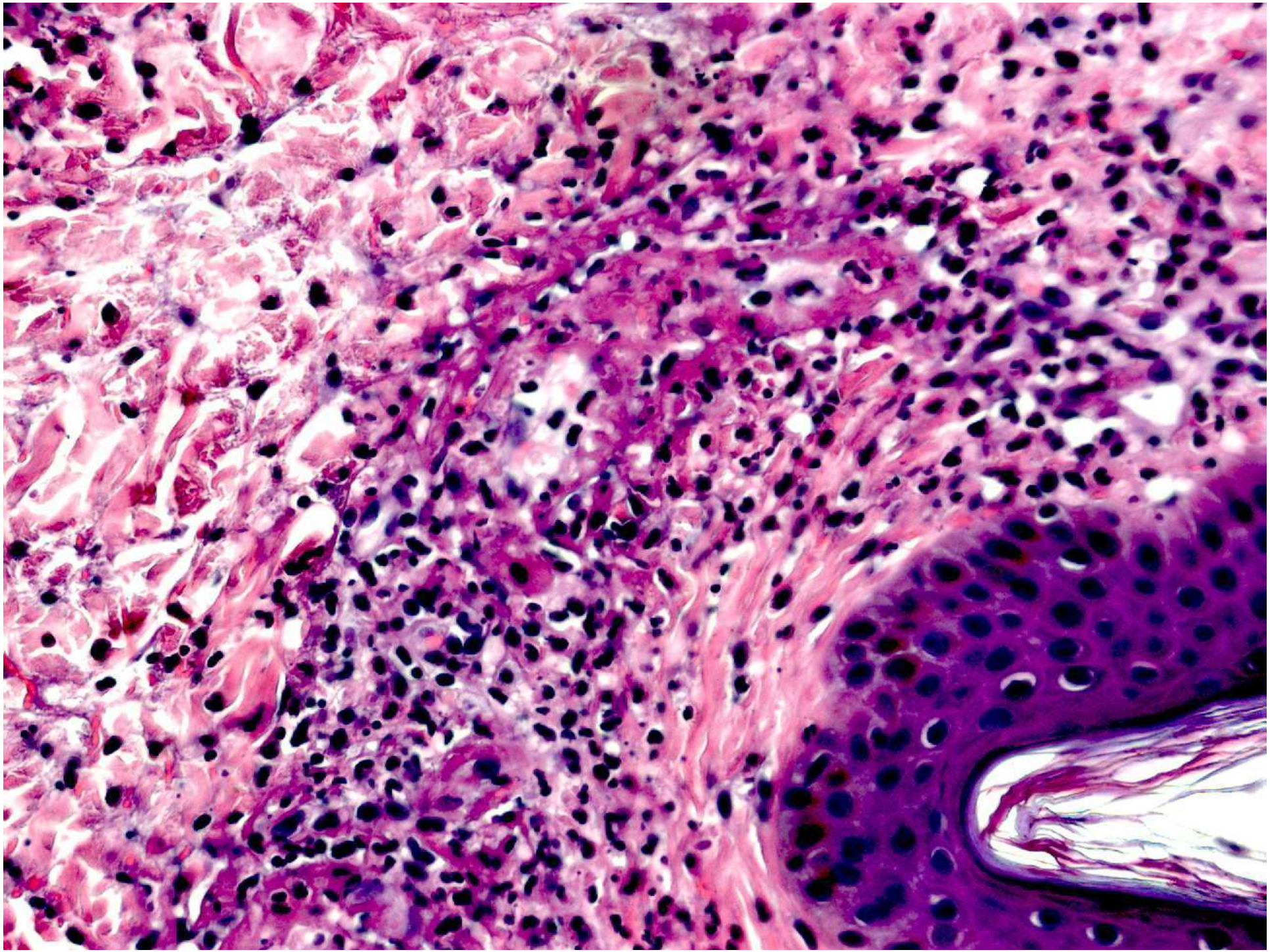


Patogenesi: migrazione leucocitaria



Patogenesi:attivazione endotelio





RECENT STUDIES OF PLEX IN AAV

Casian and Jayne, Curr Op Rheumatol 2011

Study ID	Number of patients	Study outcomes
Jayne *et al.*, 2007 RCT	137	Renal recovery at 1 year: 69% in the PLEX group 49% in non-PLEX group No difference in mortality
Walsh *et al.*, 2008 Meta-analysis	387	RR for ESRD = 0.64 in the PLEX group No difference in mortality
Szpirt *et al.*, 2010 RCT	32	Increased renal survival in the PLEX group at 1, 3, 12 months and 5 years No difference in mortality
Walters *et al.*, 2010 Meta-analysis	271	RR for ESRD = 0.47 No difference in mortality
PEXIVAS Jayne *et al.* Ongoing	500	ESRD AND mortality in the PLEX versus non-PLEX group (results awaited 2017)

RANDOMIZED CONTROLLED TRIAL of METHYLPREDNISOLONE VERSUS PLASMAPHERESIS for SEVERE RENAL VASCULITIS

Outcome	IV methylprednisolone ($n = 67$, %)	Plasmapheresis ($n = 70$, %)	P value
Renal recovery at 3 months	33 (49)	48 (68)	$P = 0.02$ (95% CI 18–35%)
Survival at 12 months	51 (76)	51 (73)	NS
ESKD at 12 months			
Overall	29 (43)	41 (59)	$P = 0.008$ (95% CI 4–40%)
Survivors	29 (57)	41 (80)	

ANCA-ASSOCIATED RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (WEGENER'S GRANULOMATOSIS)

Incidence: 0.85 per 100,000/year

Procedure	Recommendation	Category
TPE	Grade 1A	I (dialysis dependence)**
TPE	Grade 1C	I [diffuse alveolar hemorrhage (DAH)]
TPE	Grade 2C	III (dialysis independence)**

# of reported patients*: >300

RCT	CT	CS	CR	Type of evidence
8 (296)	1 (26)	22 (347)	NA	Type I

**at presentation.

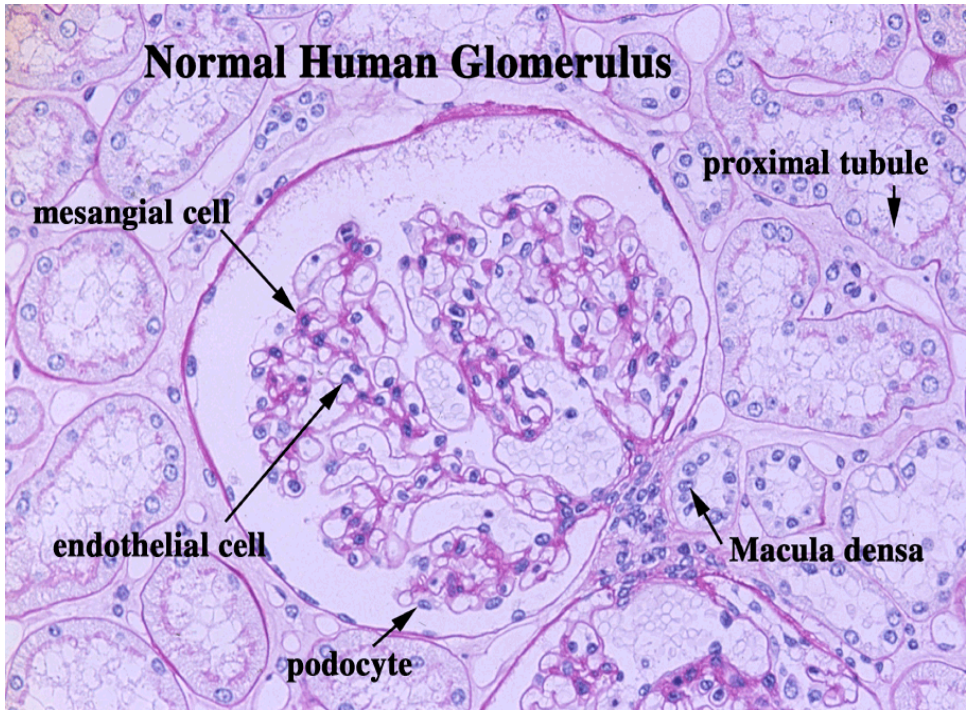
TECHNICAL NOTES

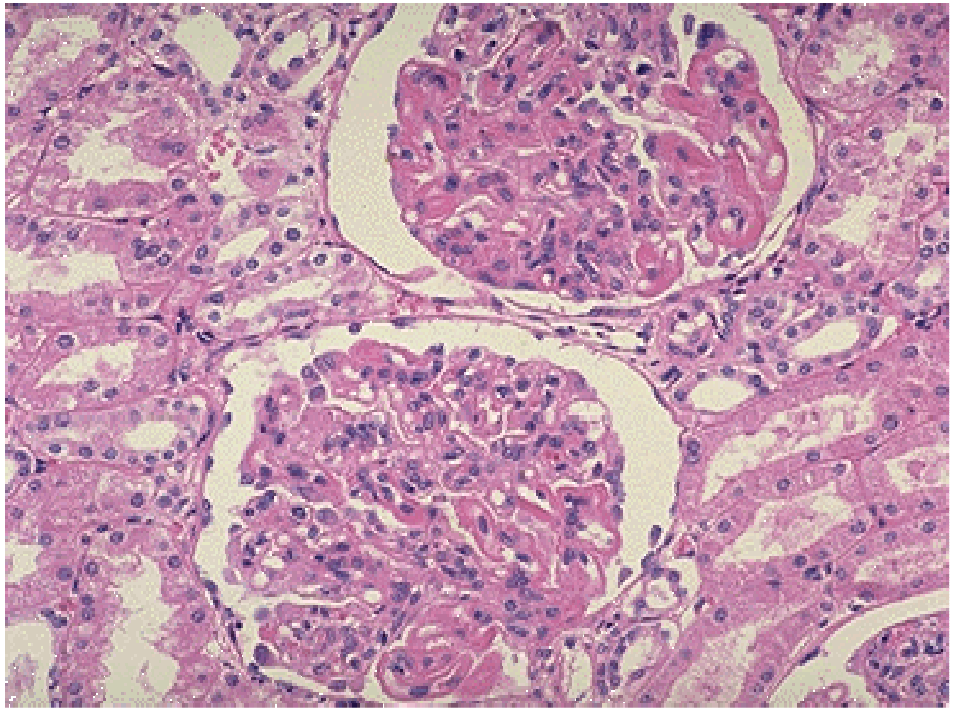
Volume treated: 1 to 1.5 TPV

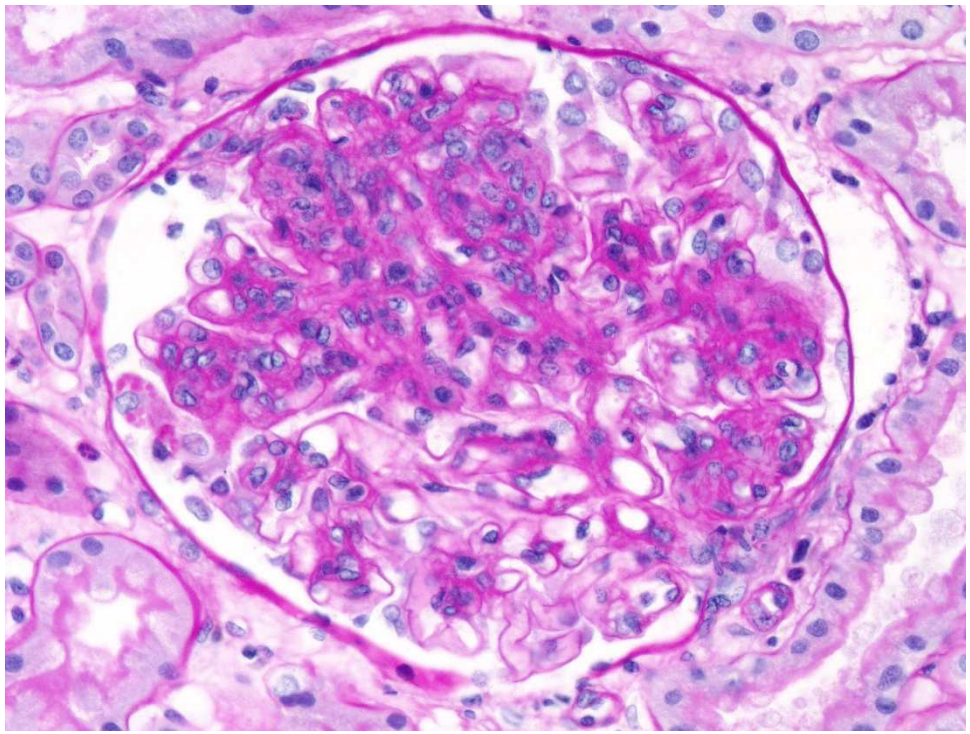
Frequency: daily or every other day

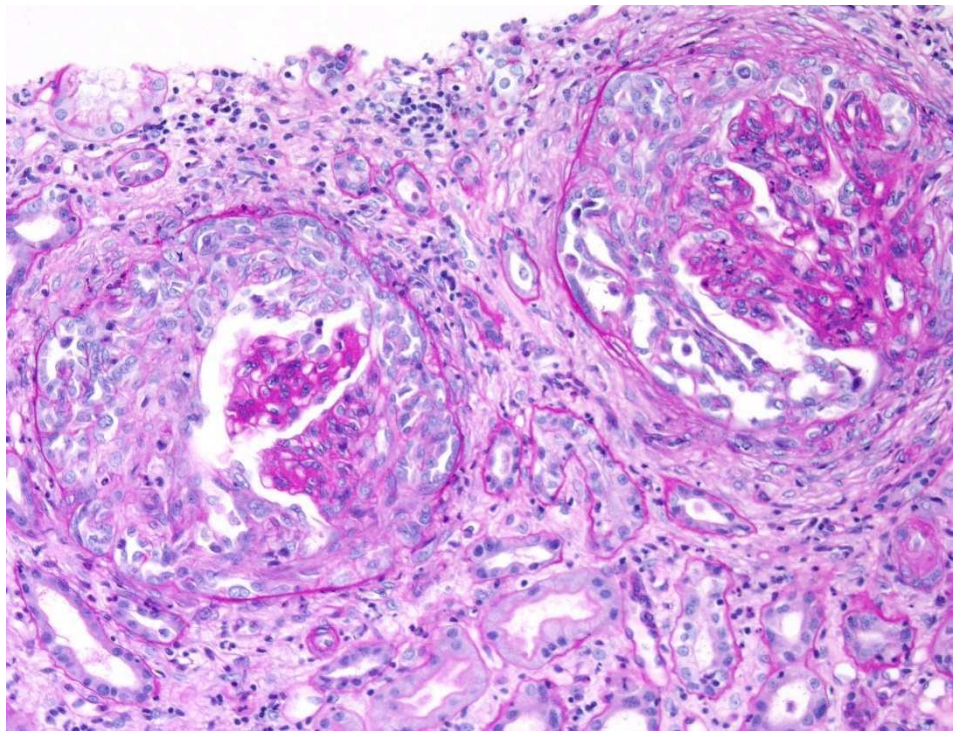
Replacement fluid: albumin; plasma when DAH present

Szczepiorkowski ZM, J Clin Apher 2010


Normal Human Glomerulus
proximal tubule
mesangial cell
endothelial cell
Macula densa
podocyte





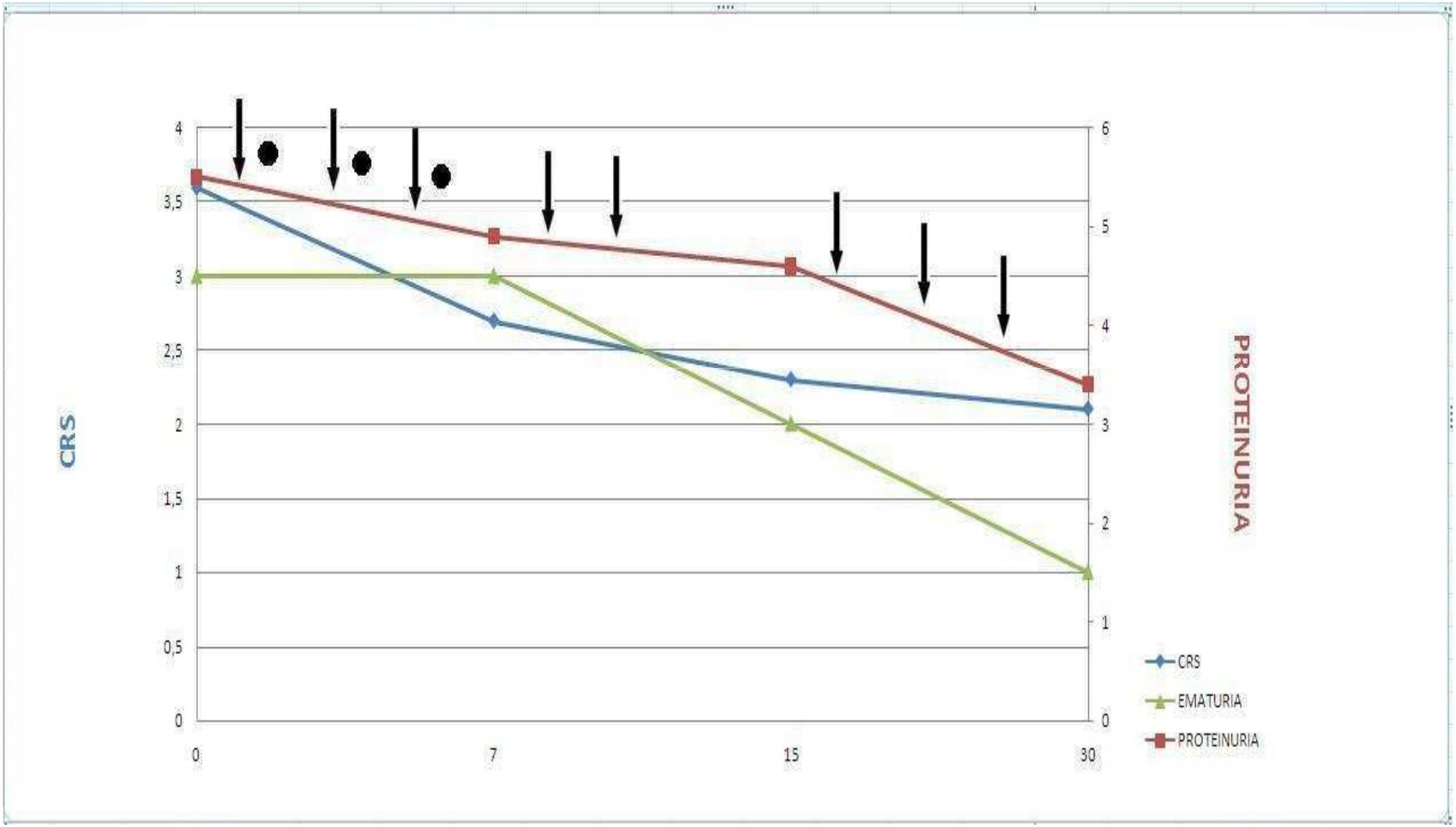


RPIgAN with >40% extracapillary proliferation

Età Sex	Mesi	Ialinosi glomerulare	Crescents floridi	Crescents sclerotici	Cr µmol/l	Proteinuria (g/24h)	Aferesi
16	0 (B)	-	90	10	884	20.6	14
M	2 (B)	10	80	10	212	2.1	8
	16 (B)	65	15	-	522	2.5	
44	0 (B)	15	40	-	106	4	11
M	2 (B)	30	10	20	97	0.8	
	6				132	2.6	
	24 (B)	45	20	-	132	4.2	
61	0 (B)	5	70	-	636	7.1	14
F	2 (B)	30	50	-	265	3.3	
39	0 (B)	35	50	-	238	5.9	10
M	2 (B)	30	30	-	230	7.9	5
	12				HD	2.5	
55	0 (B)	-	40	-	654	5.7	10
M	36				194	2	
18	0 (B)	15	80	-	265	5.1	18
F	120				371	1	

Roccatello NDT,1995

PLEX in RPIgAN with > 60% florid crescents



IMMUNE COMPLEX RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Incidence: 0.7 per 100,000/year	**Procedure**	**Recommendation**	**Category**
	TPE	Grade 2B	III

# of reported patients*: >300

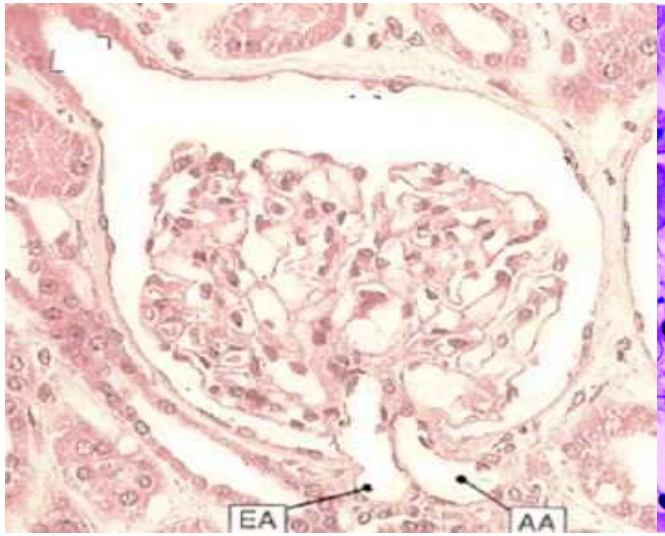
RCT	CT	CS	CR	Type of evidence
7 (196)	0	21 (295)	NA	Type I**

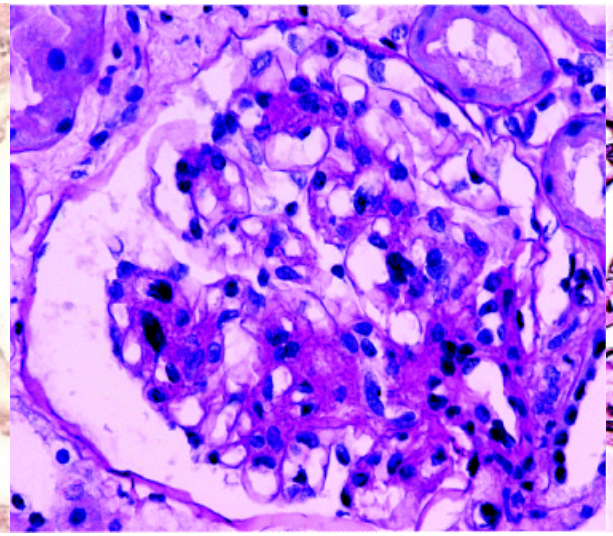
TECHNICAL NOTES

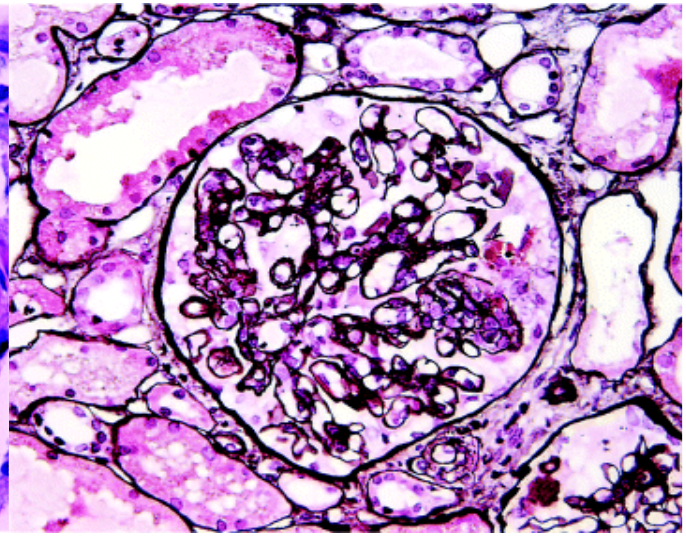
Volume treated: 1 to 1.5 TPV
Replacement fluid: albumin
Frequency: every other day

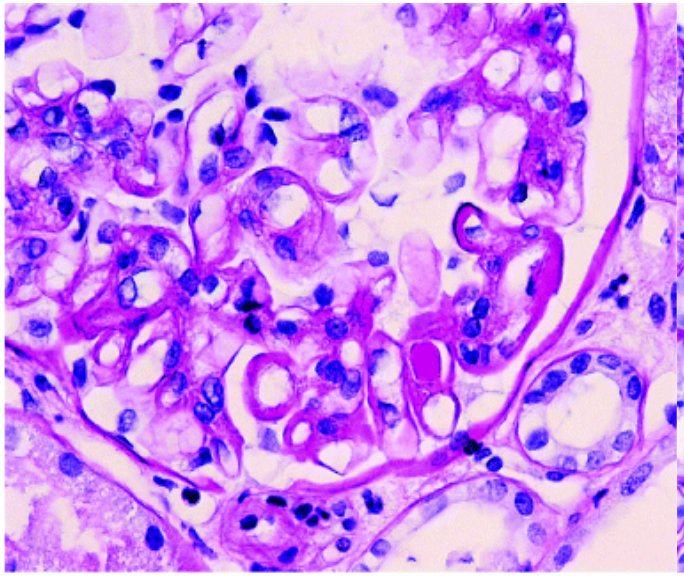
Szczepiorkowski ZM, J Clin Apher 2010

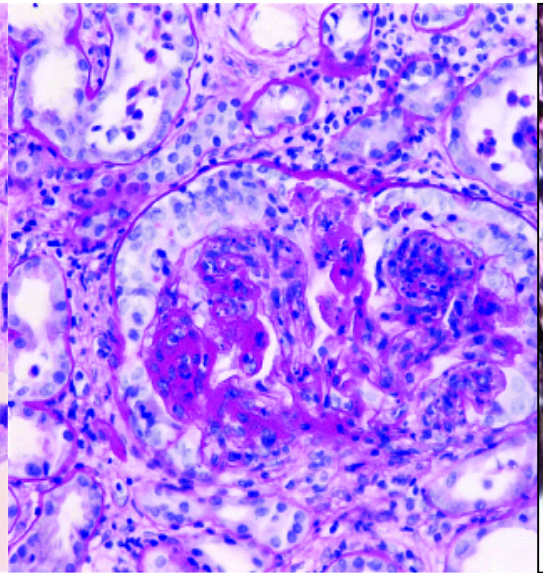
RENE NORMALE

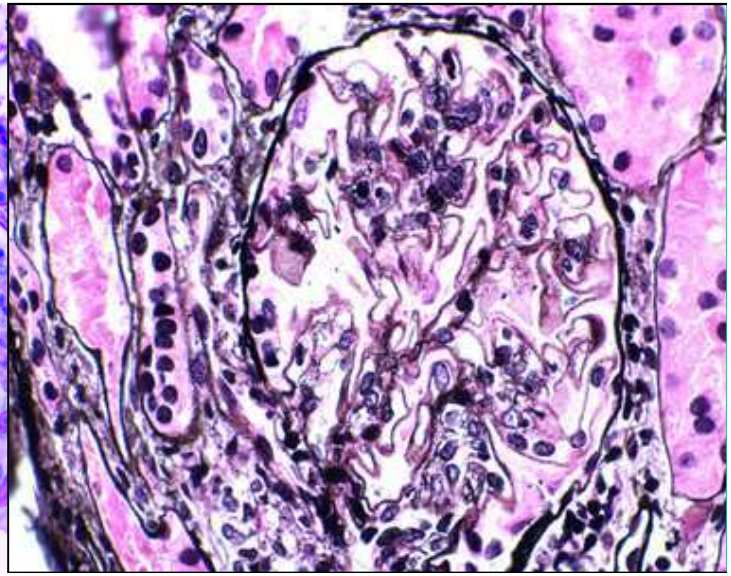












SYSTEMIC LUPUS ERYTHEMATOSUS

Incidence: 15-50 per 100,000/year

Procedure	Recommendation	Category
TPE	Grade 2C	II (severe)
TPE	Grade 1B	IV (nephritis)

# of reported patients*: >300

	RCT	CT	CS	CR	Type of evidence
TPE	1 (20)	1 (4)	14 (128)	61 (63)	Type I
TPE (nephritis)	2 (36)	2 (114)	6 (160)	10 (11)	Type I

TECHNICAL NOTES

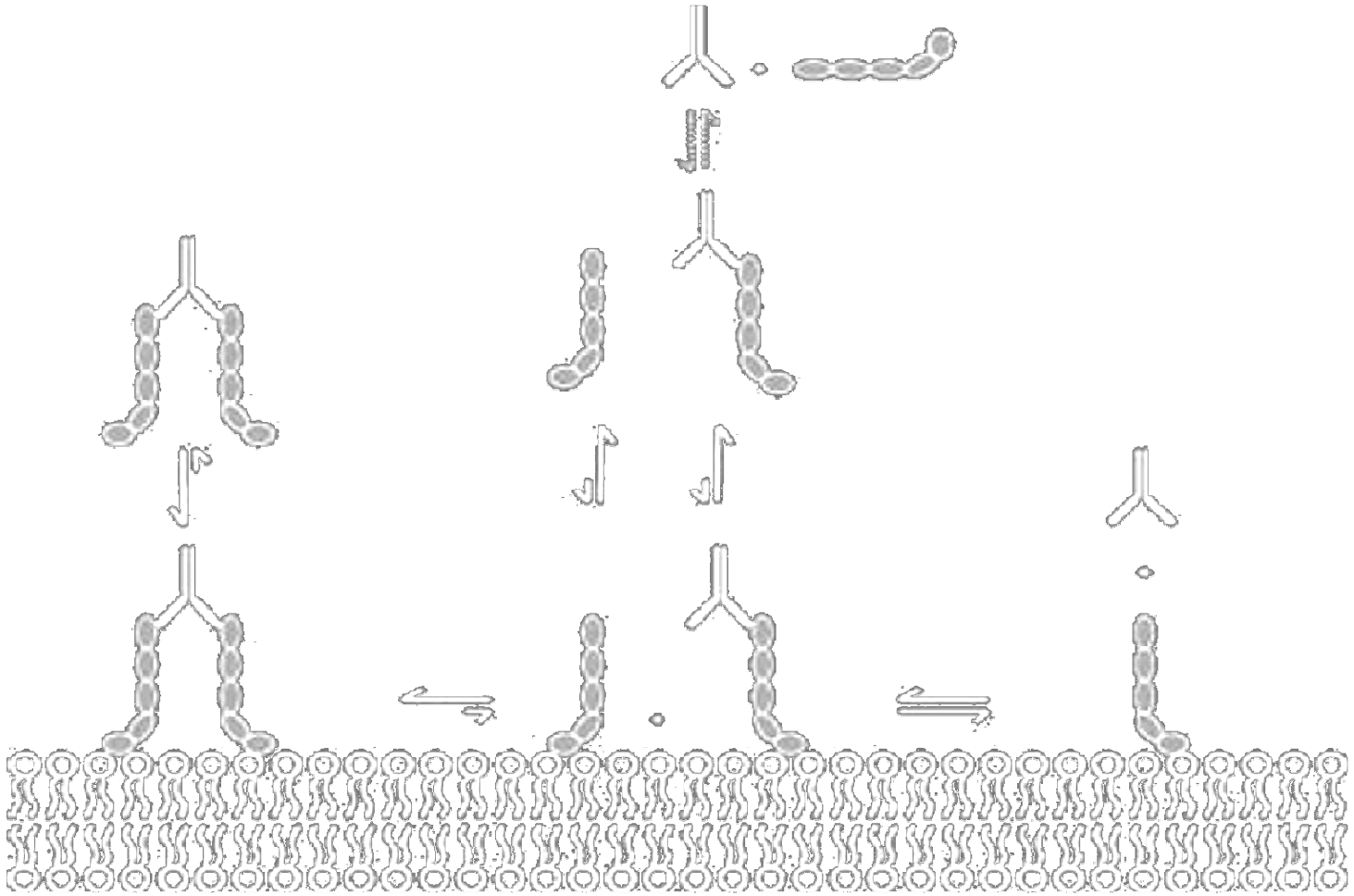
Volume treated: 1 to 1.5 TPV

Replacement fluid: albumin; plasma

Frequency: Lupus cerebritis or SLE with DAH: daily to every other day; SLE other: one to 3 times a week

Szczepiorkowski ZM, J Clin Apher 2010

Azione degli Ab antifosfolipidi



CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

Incidence: Very rare (282 cases in CAPS Registry)	**Procedure**	**Recommendation**	**Category**
	TPE	Grade 2C	II

# of reported patients*: 100–300**

RCT	CT	CS	CR	Type of evidence
0	0	6 (60)	29 (33)	Type III

**According to the CAPS Registry, 109 patients have received TPE.

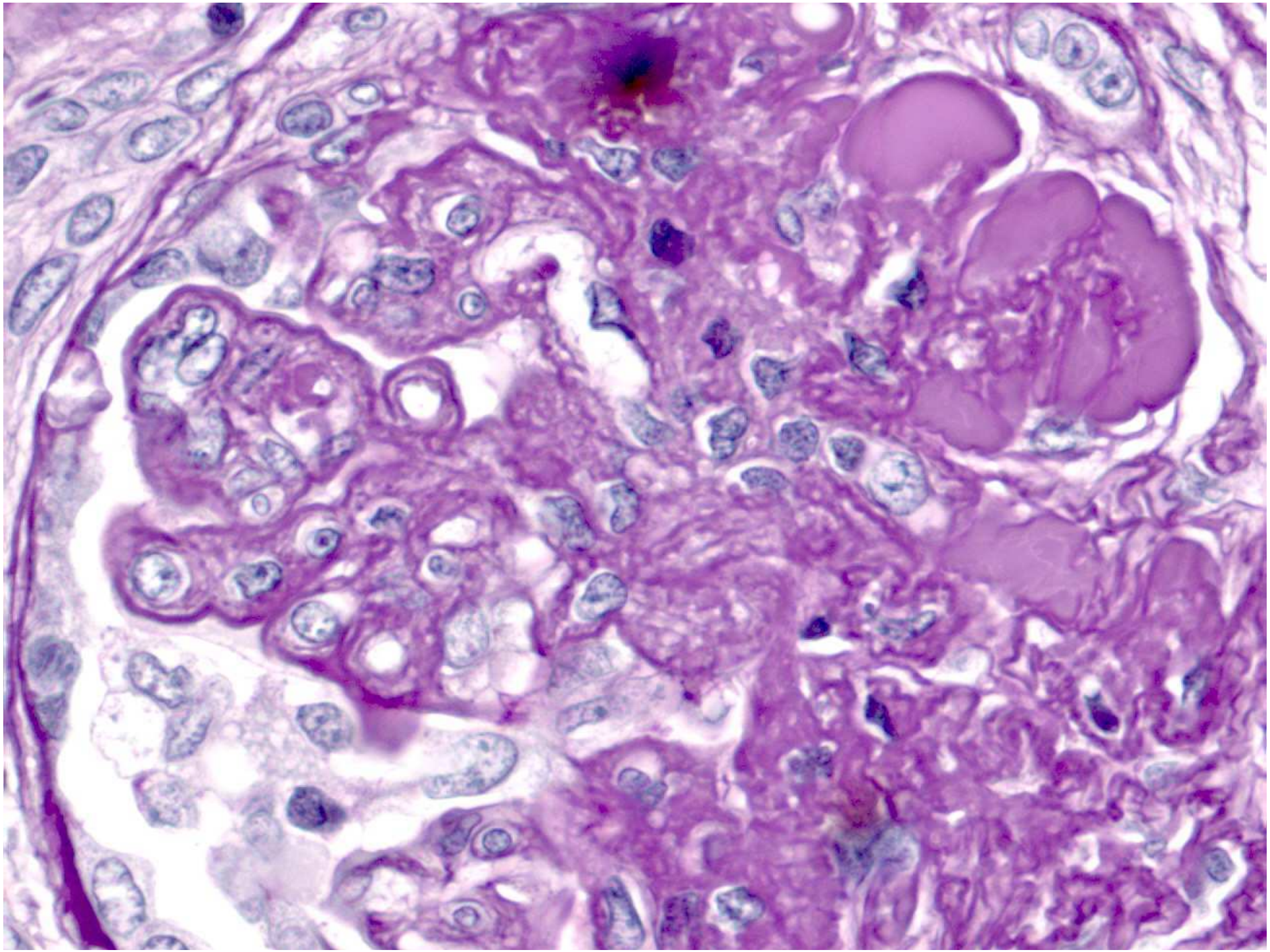
TECHNICAL NOTES

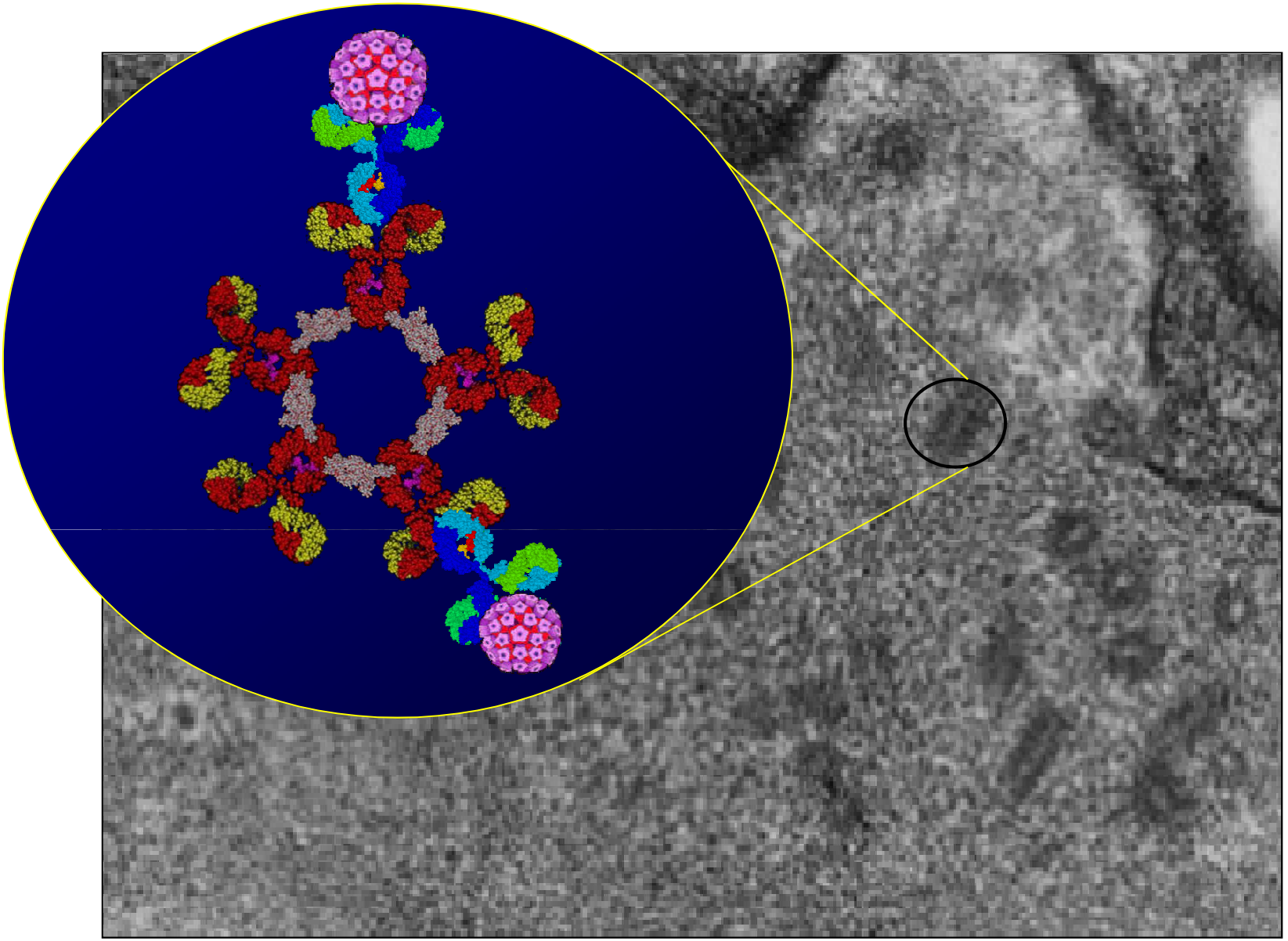
Plasma was used in most reported cases; efficacy of albumin has not been widely tested.

Volume treated: 1 to 1.5 TPV **Frequency:** daily

Replacement fluid: plasma (used in most reported cases; efficacy of albumin not tested)

Szczepiorkowski ZM, J Clin Apher 2010

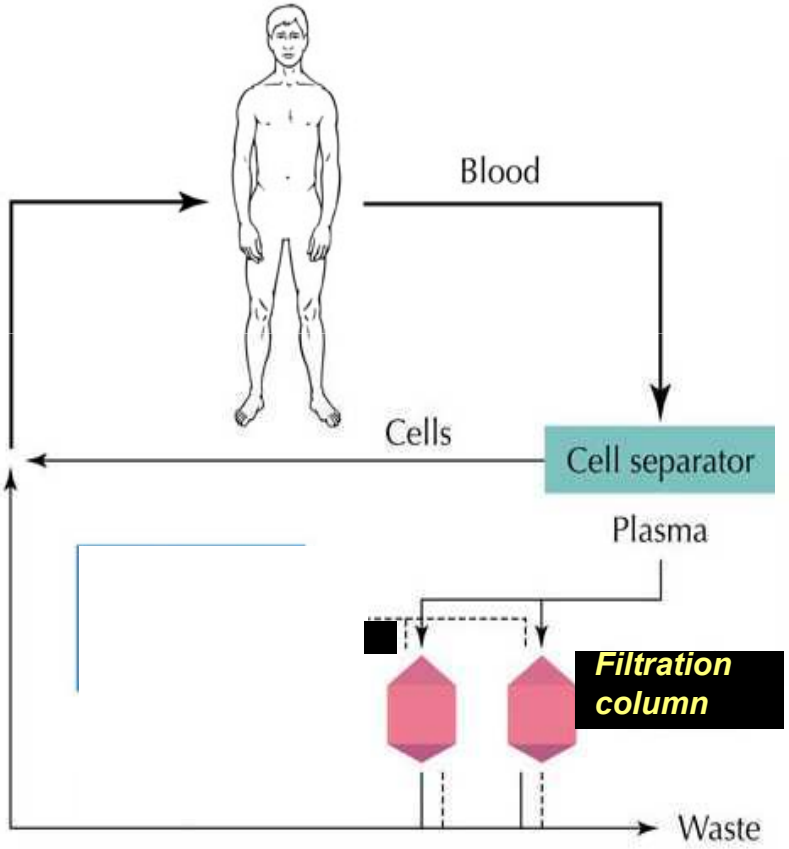




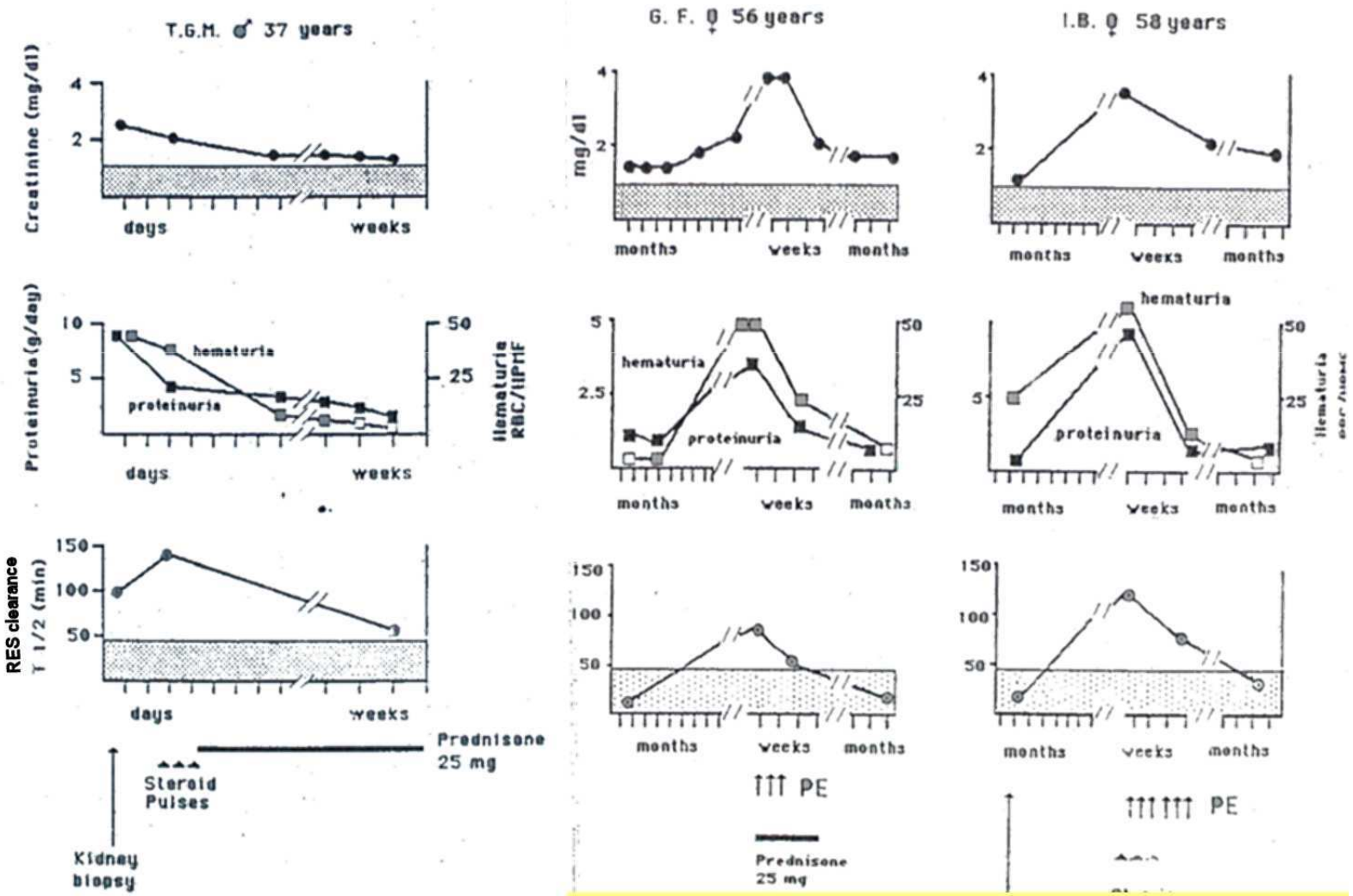
Filtrazione a cascata

Frazionamento del plasma su membrana semipermeabile

Rimozione semiselettiva di sostanze ad elevato peso molecolare



Effetto clinico ed immunologico della PE nella CM



Roccatello et al, NDT, 1991

CRYOGLOBULINEMIA

Incidence: 1-2% of patients with chronic hepatitis C, approximately 80% of patients with cryoglobulinemia have hepatitis C

Procedure	Recommendation	Category
TPE	Grade 1B	I (severe/symptomatic)
IA	Grade 2B	II (secondary to hepatitis C)

# of reported patients*: 100–300

	RCT	CT	CS	CR	Type of evidence
TPE	0	0	18 (195)	>50	Type II-3
IA	1 (17)	0	1 (4)	0	Type I

TECHNICAL NOTES

Volume treated: 1 to 1.5 TPV
Replacement fluid: albumin or plasma

Frequency: every 1 to 3 days

Szczepiorkowski ZM, J Clin Apher 2010

RCTs EVALUATING THE ROLE OF PLASMAPHERESIS IN MULTIPLE MYELOMA-ASSOCIATED RENAL FAILURE (without biopsy and biological markers)

Baweja S, J Artif Organs. 2011

Reference	Number			Dialysis-dependent at entry	Outcome	
	Total	Plasmapheresis	Control		Recovery from dialysis	Mortality
Zucchelli et al. [137]	29	15	14	24	Plasmapheresis 85%[a]	Plasmapheresis 34%[a]
					Control 18%	Control 72%
Johnson et al. [138]	21	11	10	12	Plasmapheresis 43%[b]	Plasmapheresis 25%[b]
					Control 0	Control 25%
Clark et al. [139]	97	58	39	29	Plasmapheresis 42%[b]	Plasmapheresis 33%[b]
					Control 37%	Control 33%

[a] Statistically significant difference

[b] No significant difference

Hutchison, 2007: 40 pts, 78% improvement RF if due to a cast-N and sFC dropped by >50%

Hutchison, 2009: 19 biopsy-proven cast-N pts treated with high cut-off dialyzer (interrupted in 6 for infections), 13 became HD-independent.

EuLITE trial ongoing

MYELOMA CAST NEPHROPATHY

Incidence: 1 per 100,000/year	**Procedure**	**Recommendation**	**Category**
	TPE	Grade 2B	II** (cast nephropathy)

# of reported patients*: 100-300

RCT	CT	CS	CR	Type of evidence
5 (182)	0	6 (105)	7(10)	Type I

TECHNICAL NOTES

Volume treated: 1 to 1.5 TPV
Replacement fluid: albumin; albumin/saline
Frequency: daily or every other day

Szczepiorkowski ZM, J Clin Apher 2010

HYPERVISCOSITY IN MONOCLONAL GAMMOPATHIES

Incidence: 0.1-0.3 per 100,000/year

Procedure	Recommendation	Category
TPE	Grade 1B	I** (treatment of symptoms)
TPE	Grade 1C	I** (prophylaxis for rituximab)

# of reported patients*: >300

	RCT	CT	CS	CR	Type of evidence
treatment of symptoms	0	3 (46)	18 (253)	12 (12)	Type II-1
prophylaxis for rituximab	0	0 (0)	3 (45)	2 (2)	Type II-3

TECHNICAL NOTES

Volume treated: 1 to 1.5 calculated plasma volume

Replacement fluid: albumin or albumin/saline

Frequency: daily

Szczepiorkowski ZM, J Clin Apher 2010

FOCAL SEGMENTAL GLOMERULOSCLEROSIS RECURRENT

Incidence: rare

Procedure	Recommendation	Category
TPE	Grade 1C	I

# of reported patients*: 100-300

RCT	CT	CS	CR	Type of evidence
0	2 (19)	43 (117)	8 (10)	Type II-3

TECHNICAL NOTES

Vascular access may be obtained through arteriovenous fistulas or grafts used for dialysis.

Volume treated: 1 to 1.5 TPV

Frequency: daily or every other day

Replacement fluid: albumin or albumin/plasma

Szczepiorkowski ZM, J Clin Apher 2010

BLOOD, 15 MARCH 2004 • VOLUME 103, NUMBER 6

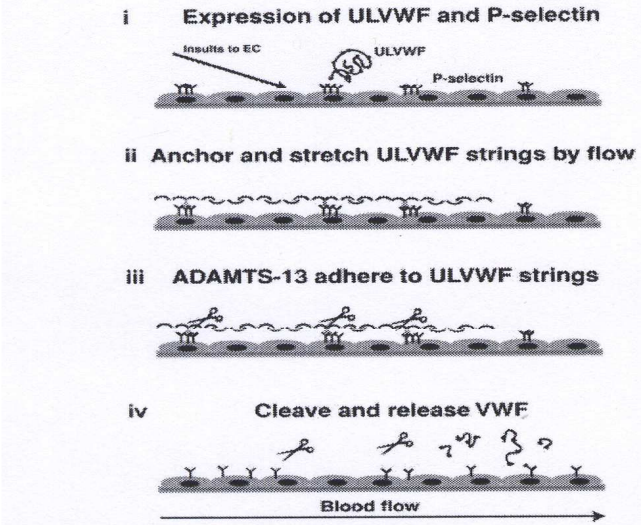
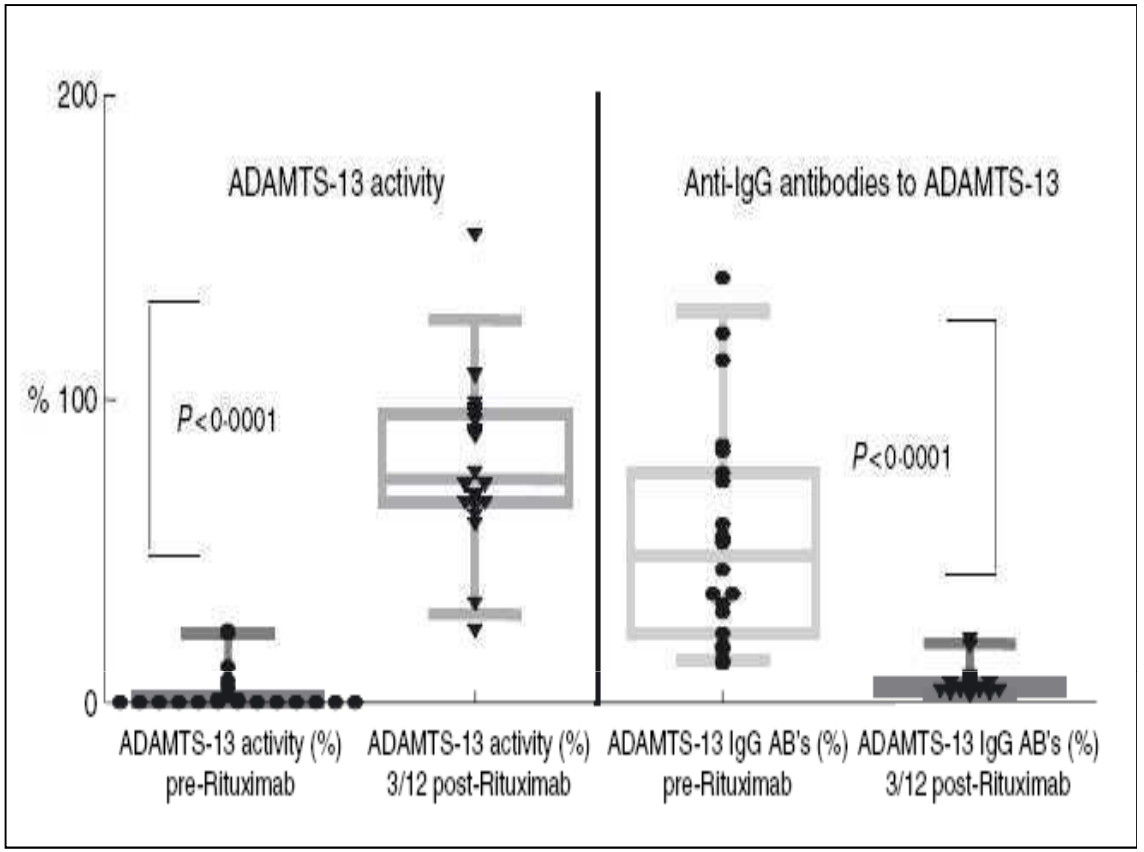


Figure 7. Schematic illustration of a potential mechanism of cleavage of ULVWF string by ADAMTS-13 metalloprotease. On stimulation, endothelial cells release contents from the Weibel-Palade bodies. Membrane-bound P-selectin anchors ULVWF multimers to the surface of endothelial cells to allow long stringlike structures to form under flow. Fluid shear stress stretches these strings to expose sites for ADAMTS-13 to adhere to ULVWF and/or cleavage site in the A2 domain of ULVWF. The cleavage releases ULVWF from endothelial cells (and from wall shear stress) to allow cleaved VWF to adopt different conformation that is no longer



A disintegrin and metalloproteinase with thrombospondin motif-13 (ADAMST-13) activity and anti-ADAMST-13 in 25 pts with acute refractory /relapsing idiopathic TTP treated with Rituximab mmediately following PE. All 25 pts attained complete clinical and labotatory remission in a medianof 11 days.

***No relapses were observed* (Scully, BJH, 2006)**

THROMBOTIC THROMBOCYTOPENIC PURPURA

Incidence: 0.37/100,000/year in the US **Procedure** TPE **Raccomendation** Grade 1A

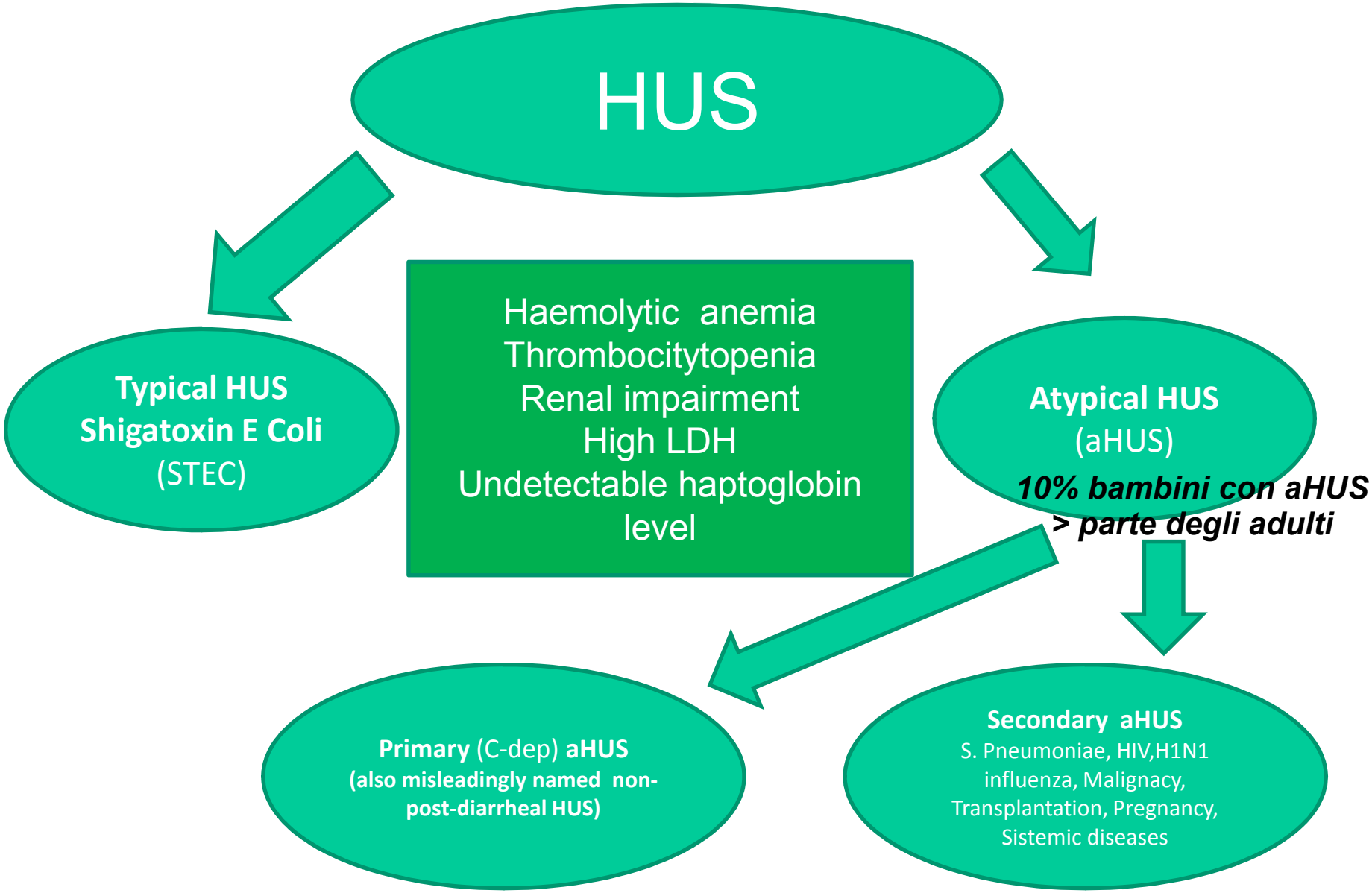
# of reported patients: > 300

RCT 7 (301) **CT** 2 (133) **CR** 17 (915) **CR** 28 (48) **Type of evidence I**

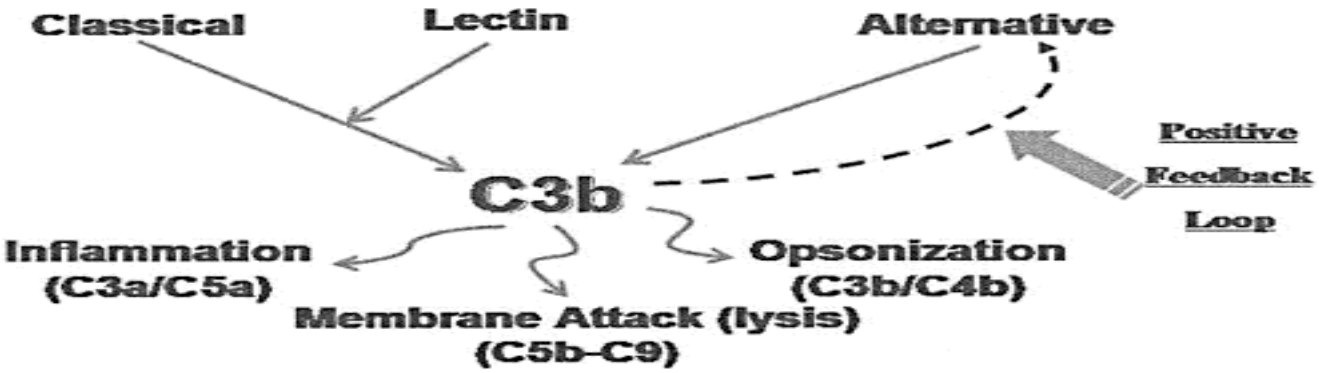
TECHNICAL NOTES

Volume treated 1-1.5 TPV
Replacement fluid plasma, plasma cryoprecipitate removed

Szczepiorkowski ZM, J Clin Apher 2010


HUS
Haemolytic anemia
Thrombocitytopenia
Renal impairment
High LDH
Undetectable haptoglobin level
Typical HUS
Shigatoxin E Coli
(STEC)
Atypical HUS
(aHUS)
10% bambini con aHUS
> parte degli adulti
Primary (C-dep) aHUS
(also misleadingly named non-post-diarrheal HUS)
Secondary aHUS
S. Pneumoniae, HIV,H1N1 influenza, Malignacy, Transplantation, Pregnancy, Sistemic diseases

Complement activation



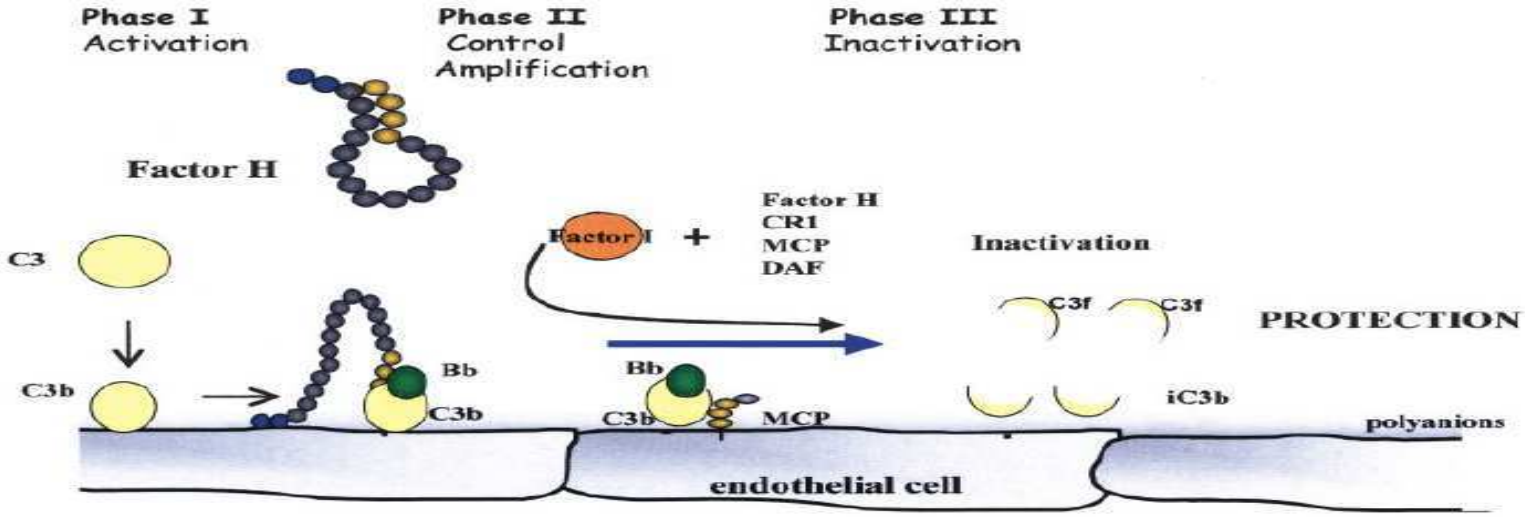


Table 1. Classification of Atypical Hemolytic–Uremic Syndrome.*

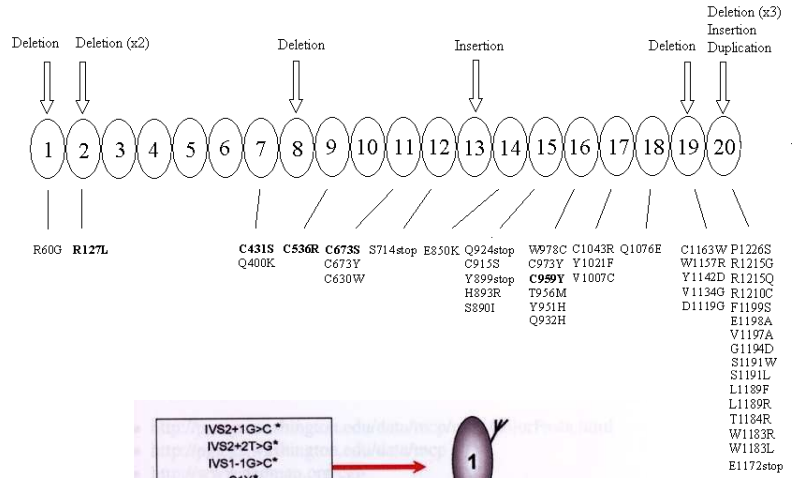
Form of Disease	Complement Abnormalities
Familial	Mutations in *CFH*, 40–45%; in *CFI*, 5–10%; in *C3*, 8–10%; in *MCP*, 7–15%; in *THBD*, 9%; and in *CFB*, 1–2%.
Sporadic	
Idiopathic	Mutations in *CFH*, 15–20%; in *CFI*, 3–6%; in *C3*, 4–6%; in *MCP*, 6–10%; in *THBD*, 2%; and in *CFB*, 2 cases; anti-CFH antibodies: 6–10%
Pregnancy-associated	Mutations in *CFH*, 20%; in *CFI*, 15%
HELLP syndrome	Mutations in *CFH*, 10%; in *CFI*, 20%; and in *MCP*, 10%
Drugs	Rare *CFH* mutations (mostly unknown)
Organ transplantation	Mutations in *CFH*, 15%; in *CFI*, 16%
Human immunodeficiency virus infection	Unknown†
Cancer	Unknown†

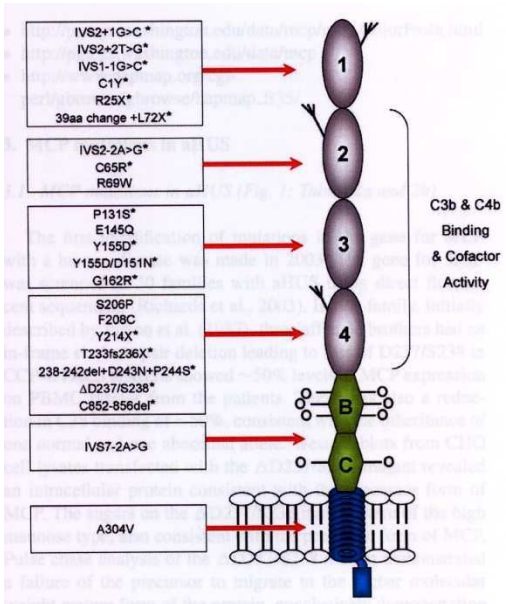
* HELLP denotes hemolytic anemia, elevated liver enzymes, and low platelet count.

† There are no published data on the frequency of complement gene mutations or anti-CFH autoantibodies in patients with this condition.

Short Consensus Repeats 1-4 binds to C_3b

SCR19-20 binds to polyanionic surface-bound C_3B





	CFH mutation	CFI mutation	MCP mutation	C3 mutation	CFB mutation	Anti CFH Ab
Decreased [C3]	***50%***	***30%***	***2%***	***80%***	***100%***	***60%***

Table 3 Main clinical characteristics of patients with atypical hemolytic uremic syndrome according to complement abnormality

Gene or subgroup	Frequency in aHUS	Minimal age at onset		Risk of death or ESRD at 1st episode or within < 1 y	Risk of relapses	Risk of recurrence after renal transplantation	Plasma therapy indicated
		Children	Adults				
CFH	20-30%	Birth	any age	50-70%	50%	75-90%	Yes
CFI	4 -10%	Birth	any age	50%	10-30%	45-80%	Yes
MCP	5 -15%	> 1 y	any age	0-6%	70-90%	< 20%	Questionable
C3	2 -10%	7 m	any age	60%	50%	40-70%	Yes
CFB	1-4%	1 m	any age	50%	3/3 not in ESRD	100%	Yes
THBD	3 -5%	6 m	rare	50%	30%	1 patient	Yes
Anti-CFH Ab	6%	Mostly 7-11 y		30-40%	40-60%	Yes if high Ab titer	Yes (+ IS)

Loirat and Fremeaux-Bacchi Orphanet Journal of Rare diseases 2011 6:60

Terapia: plasma exchange

- ***Terapia 1 scelta dal 2010***
- ***Riduzione delle mortalità dal 50% al 25%***
- ***Somministrazione con plasma di CFH,CFB,CFI, C3***
- ***Rimozione di ab anti CFH***
- ***Rimozione di CFH,CFI,CFB modificati***
- ***Preferito alla plasmaterapia***

Plasmatherapy in Atypical Hemolytic Uremic Syndrome Chantal Loirat[1], Arnaud Garnier[1], Anne-Laure Sellier-Leclerc[1],Theresa Kwon Assistance Publique-Hôpitaux de Paris, Pediatric Nephrology Department, Université Paris-Diderot, Hôpital Robert Debré, Paris, Francea plasmaterapia

HEMOLYTIC UREMIC SYNDROME

Incidence:	Procedure	Recommendation	Category
Diarrhea-associated HUS: 6.1/100,000 children under 5 years (overall incidence: 1–2/100,000)	TPE	Grade 2C	II (aHUS due to complement factor gene mutations)
Prevalence of Atypical HUS: 3.3 per 1,000,000 in those <18 y.o.	TPE	Grade 2C	I (aHUS due to autoantibody to factor H)
	TPE	Grade 1C	IV (d+HUS or typical HUS)

# of reported patients*: >300

	RCT	CT	CS	CR	Type of evidence
aHUS due to complement factor gene mutations	0	0	2 (6)	20 (25)	Type III
aHUS due to autoantibody to factor H	0	0	2 (6)	2 (2)	Type III
d+HUS or typical HUS	0	0	4 (48)	4 (4)	Type II-3

TECHNICAL NOTES

Volume treated: 1 to 1.5 TPV **Frequency:** daily

Replacement fluid: plasma or albumin (T activation associated HUS)

Szczepiorkowski ZM, J Clin Apher 2010

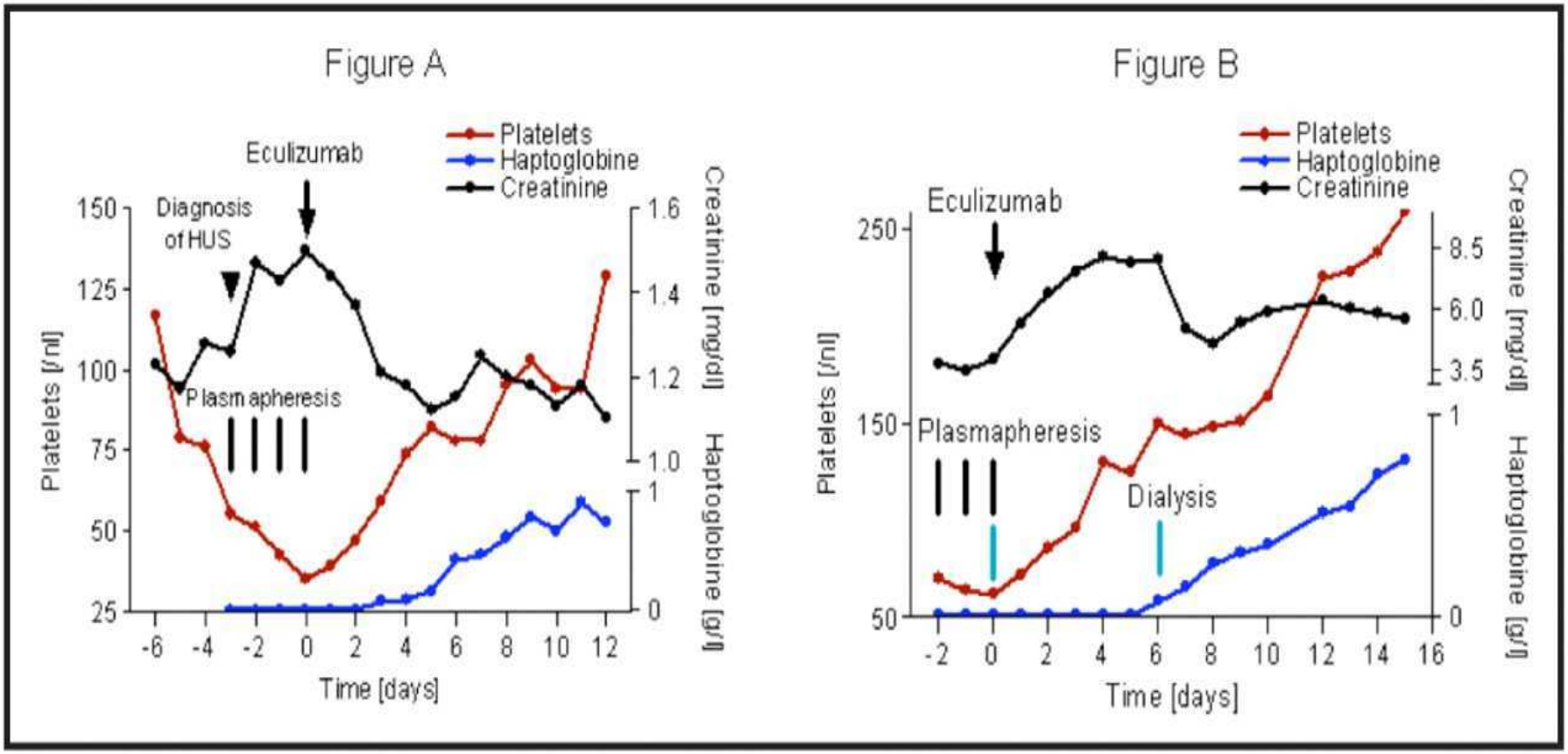
Terapia: plasma exchange

Response to PEX

CFH: 63%
CFI: 25%
MCP: 90% spontaneous remissions
frequent relaples
C3, CFB: 55%
THBD: 85%
Anti-CFH: 1rst line (plus immunosuppressants)

Loirat and Fremeaux-Bacchi Orphanet Journal of Rare diseases 2011 6:60

- Iniziare terapia appena possibile (massimo entro 24 ore) proseguendo quotidianamente
- All'inizio scambiare 1,5 VP (60-75 ml/Kg)
- Lo scambio deve essere plasma con plasma
- Se non possibile PEX iniziare con infusione di plasma (10-15 ml/Kg)
- Se persistenza emolisi o mancata ripresa funzionale (anche a PTL normalizzate) proseguire con PE quotidiana o passare ad altra terapia
- Mutazione MCP: stop PEX; Mutazione CFH o CFI+ C3 o CFB: proseguire *a priori* indefinitamente



Successful Treatment of Atypical Hemolytic Uremic Syndrome with the Complement Inhibitor Eculizumab.

Jens Nuernberger1,*, Oliver Witzke1,*, Russell P. Rother, PhD2,*, Thomas Philipp1,*, Udo Vester1,*, Hideo Baba1,*, Lothar Bernd Zimmerhackl3,* and Andreas Kribben1,*

Blood (ASH Annual Meeting Abstracts) 2008 112: Abstract 2294