HEL(L)P ?!

when extensive laboratory diagnostics are required

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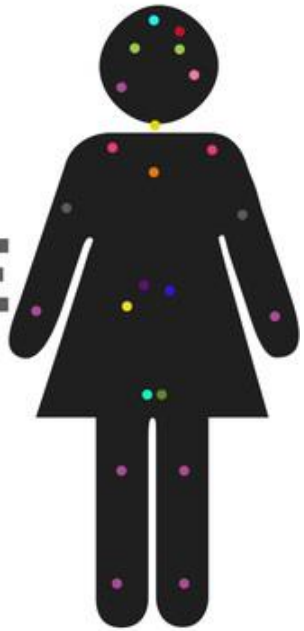
48,000

WOMEN PER YEAR WILL DEVELOP HELLP SYNDROME. IF HELLP GOES UNTREATED IT CAN CAUSE DEATH. DO YOU KNOW WHAT TO LOOK FOR? OR WILL IT BE TOO LATE?

VISION PROBLEMS
SEVERE HEADACHES
SEIZURE
NECK PAIN
SHOULDER PAIN
CHEST TENDERNESS
HIGH BLOOD PRESSURE
VOMITING
NAUSEA
PROTEIN IN URINE
BLEEDING
FATIGUE
SWELLING
ABDOMINAL PAIN (RIGHT SIDE)



TO LEARN MORE VISIT
WWW.WHATTHEHELLP.COM

WTH?

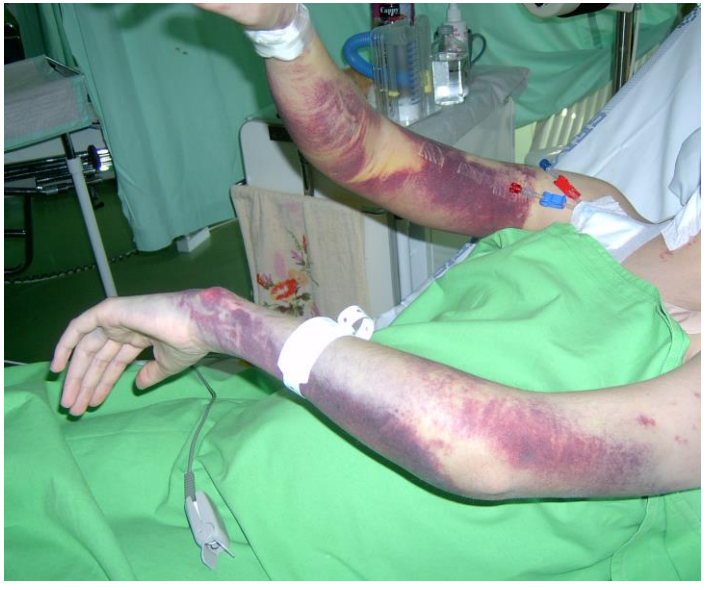
Haemolysis, elevated liver enzymes, low platelet (HELLP)

- A variant of pre/eclampsia
- Incidence: 0.17-0.9% of all pregnancies; 19-27% of subsequent pregnancies
- 1/4 of preeclamptic cases
- Main characteristic: endothel dysfunction
- Therapy: termination of pregnancy, plasmapheresis, steroid (?), $MgSO_4$
- Mortality 1,1%-**86%** ???

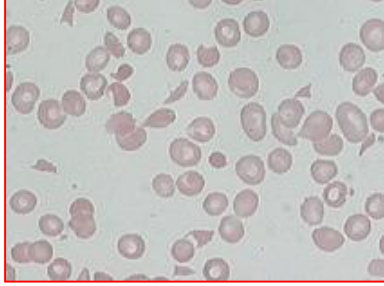
Aloizos S et al. J Obstet Gynaecol. 2013 May;33(4):331-7.

27 years old primipara

- Admission on the 40th week of an eventless pregnancy due to eclampsia, low Hgb, platelet count, elevated liver enzymes, LDH, with suspicion of HELLP-sy
- Urgent caesarean section (transfusion:10E Plt), intraoperative convulsion
- 2700g, living, retarded boy
- Transmission to our department



HELLP severity

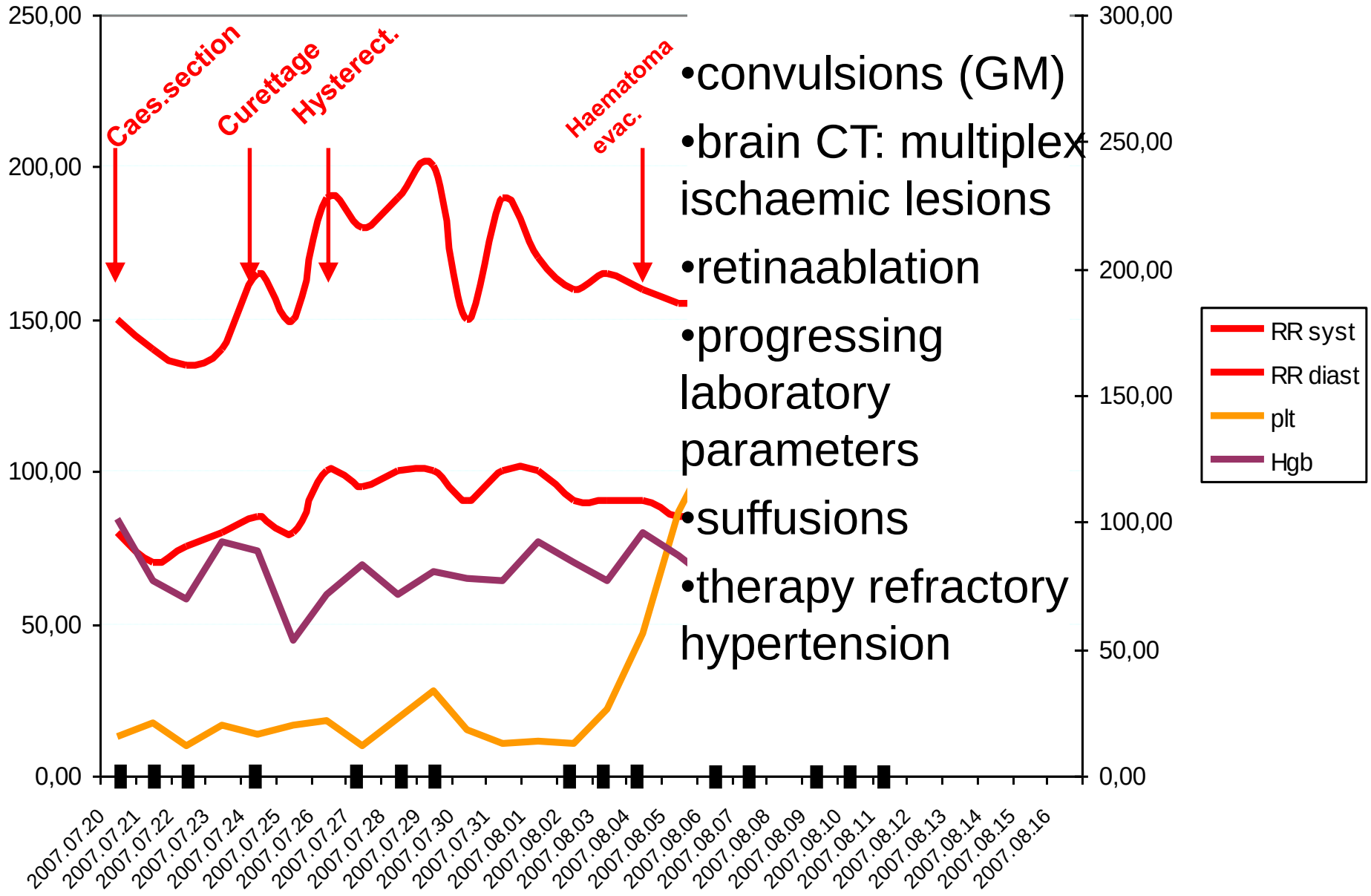


HELLP class	Tennessee classification	Mississippi classification
1	PLTs $\leq 100 \times 10^9$/l AST ≥ 70 IU/l LDH ≥ 600 IU/l	PLTs $\leq 50 \times 10^9$/l AST or ALT ≥ 70 IU/l LDH ≥ 600 IU/l
2		PLTs $\leq 100 \times 10^9$/l and $\geq 50 \times 10^9$/l AST or ALT ≥ 70 IU/l LDH ≥ 600 IU/l
3		PLTs $\leq 150 \times 10^9$/l and $\geq 100 \times 10^9$/l AST or ALT ≥ 40 IU/l LDH ≥ 600 IU/l

Haptoglobin ↓

Plasma free haemoglobin ↑

Madách K et al. Eur J Obstet Gynecol Reprod Biol. 2008 Aug;139(2):133-8
Aloizos S et al. J Obstet Gynaecol. 2013 May;33(4):331-7.


Caes.section
Curettage
Hysterect.
Haematoma evac.
•convulsions (GM)
•brain CT: multiplex ischaemic lesions
•retinaablation
•progressing laboratory parameters
•suffusions
•therapy refractory hypertension
250,00
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150,00
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300,00
250,00
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50,00
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RR diast
plt
Hgb
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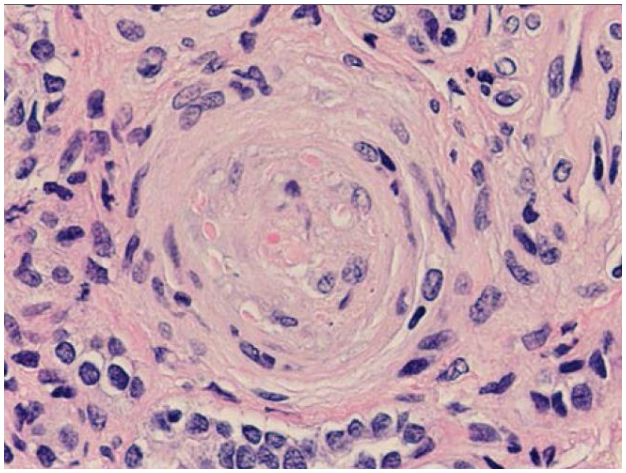
2007.08.16

Thrombotic microangiopathies (9)

- Hereditary (mutations)
  - ADAMTS13 deficiency (TTP)
  - Complement-mediated
  - Metabolism-mediated
  - Coagulation-mediated



- Acquired
  - ADAMTS13 deficiency (TTP)
    - autoantibodies
  - Shiga-toxin (ST-HUS)
    - E.coli, Shigella dysenteriae
  - Drug-mediated (immune)
    - antibodies
  - Drug-mediated (toxic dose)
    - VEGF inhibition
  - Complement-mediated (A-HUS)
    - compl.factor H activity inhibition by antibodies

George JN et al. N Engl J Med. 2014 Aug 14;371(7):654-66.

Thrombotic microangiopathies (9)

- Hereditary (mutations)
  - ADAMTS13 deficiency (TTP)
    - Plasma infusion
  - Complement-mediated
    - Plazma inf, PEX, anticomplement agent
  - Metabolism-mediated
    - Vitamin B12, folinic acid
  - Coagulation-mediated
    - Plasma infusion

- Acquired
  - ADAMTS13 deficiency (TTP)
    - PEX, immunosuppression
  - Shiga-toxin (ST-HUS)
    - Supportive care
  - Drug-mediated (immune)
    - Removal of drug, supportive
  - Drug-mediated (toxic dose)
    - Removal of drug, supportive
  - Complement-mediated (A-HUS)
    - PEX, immunosuppression, anticomplement agent

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Available research laboratory tests

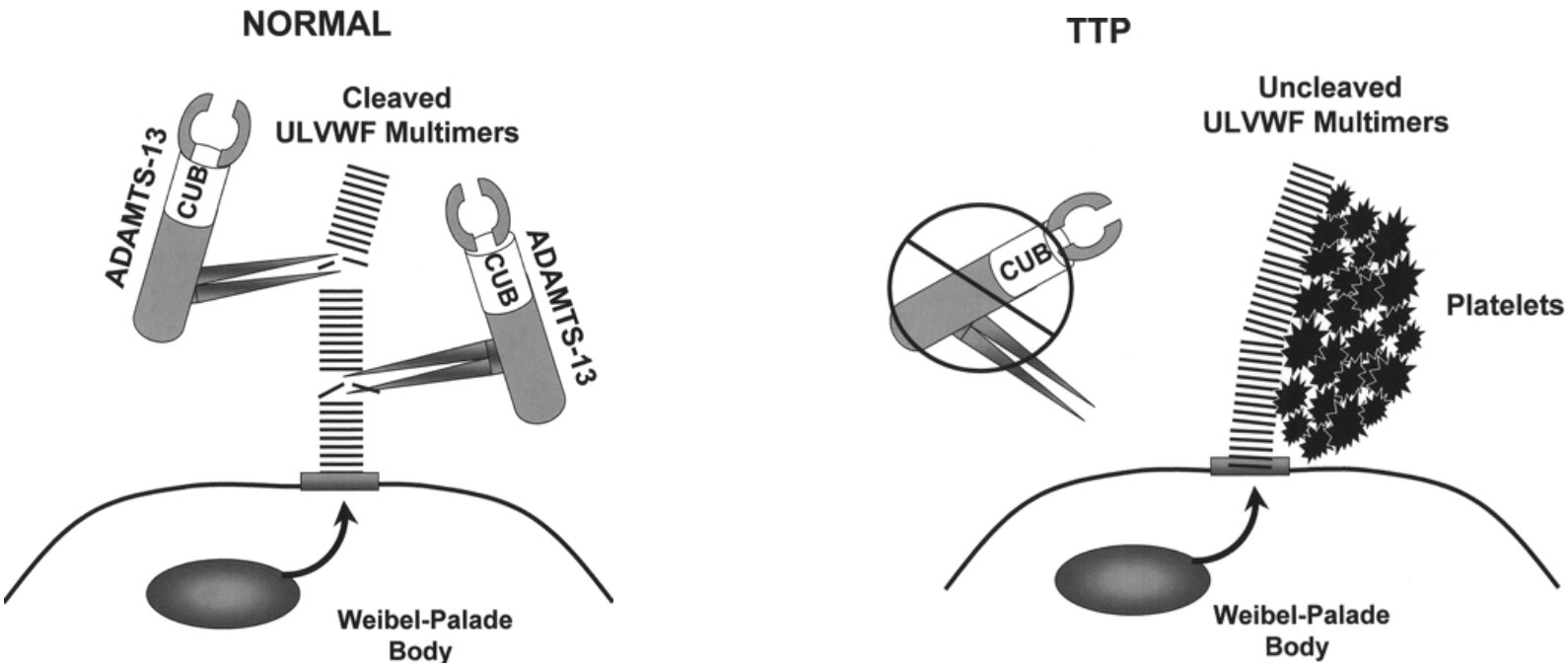
TTP: ADAMTS13 activity, anti-ADAMTS13 antibody measurement, genetics

- ADAMTS13 metalloprotease enzyme activity
  - FRET-vWF73: Kinetic fluorimetric assay
- Functional measurement of inhibitory antibodies : Bethesda unit (BU)
- *ADAMTS13* mutation screening

HUS: complement factor, antibody measurement, genetics

- Functional measurement of complement activity
  - CH50 and WIELISA-ALT
- Complement protein measurement
  - C3, C4, FH, FB, FI
- Mutation screenings
  - *CFH* exons 2, 4, 6, 9 14-15, 17, 18, 20-23, *CFI* exons 3, 5-6, 9-10, 12-13, *CD46* exons 5-6, *C3* exons 14, 20, 26-27, 37, *CFB* exons 6-7, *THBD* in progress
- Haplotype analysis
  - *CFH* tag SNPs, *MCP* tag SNPs
- Detection of copy number variation in region 1q32 (MLPA)
- Anti-HF IgG measurement to detect autoimmune form

The molecular cause of TTP is the procoagulant transformation of the endothelial surface due to formation of immature vWF

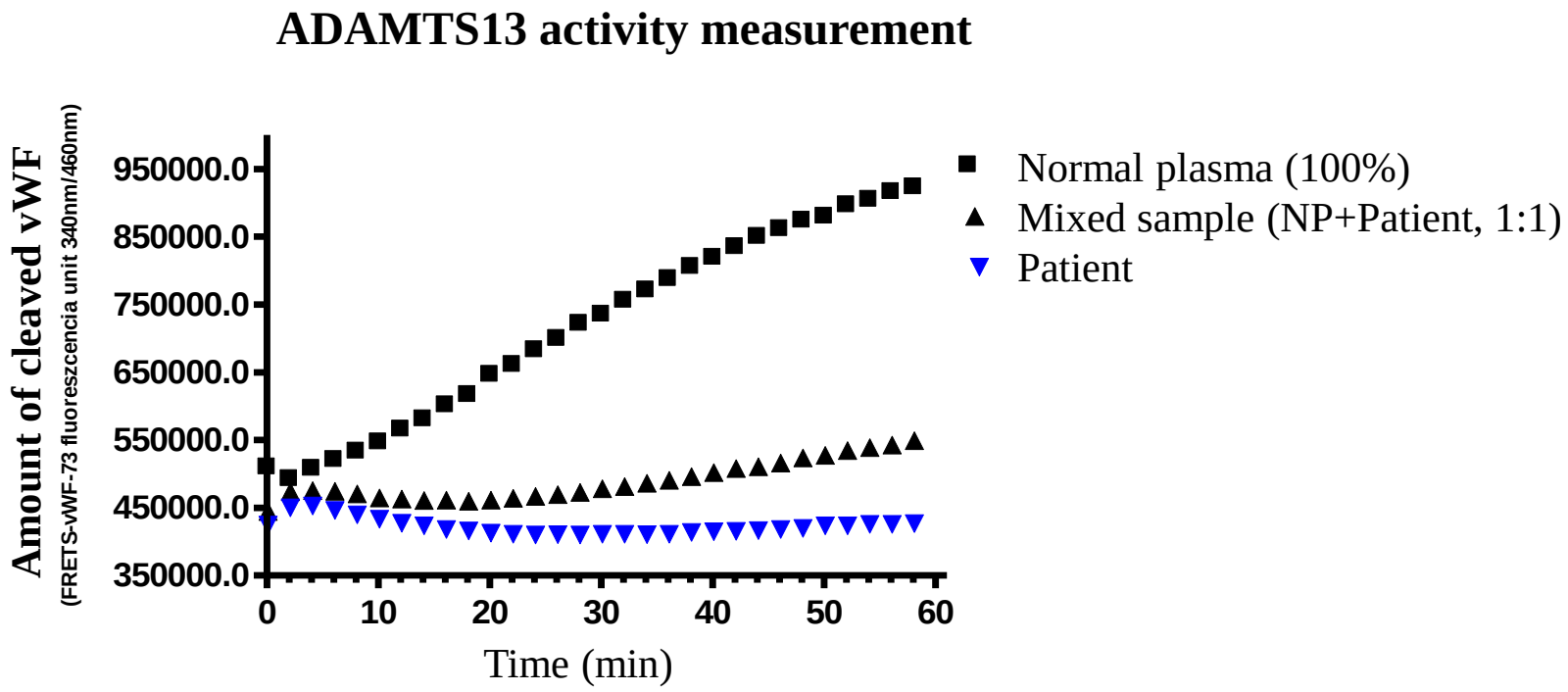


Acute mortality with PEX 20% (without PEX 90%)

Moake JL. Semin Hematol. 2004 Jan;41(1):4-14.
Réti M et al. J Thromb Haemost. 2012 May;10(5):791-8.

ADAMTS13 activity
Fluorescence resonance energy transfer (FRET)

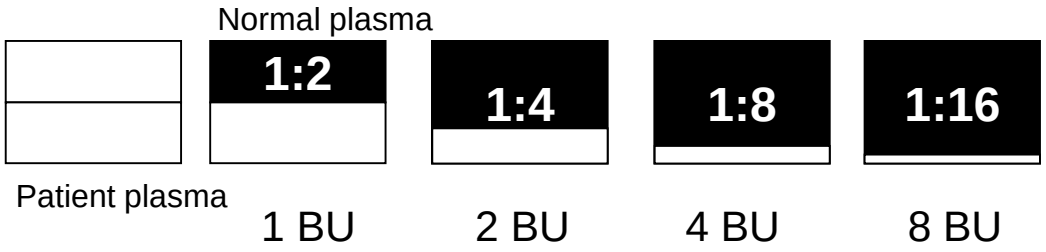
- We found 0% activity in the plasma of the patient even after several PEXs
- Mixing study demonstrated the presence of anti-ADAMTS13 inhibitory antibodies (activity 0%)

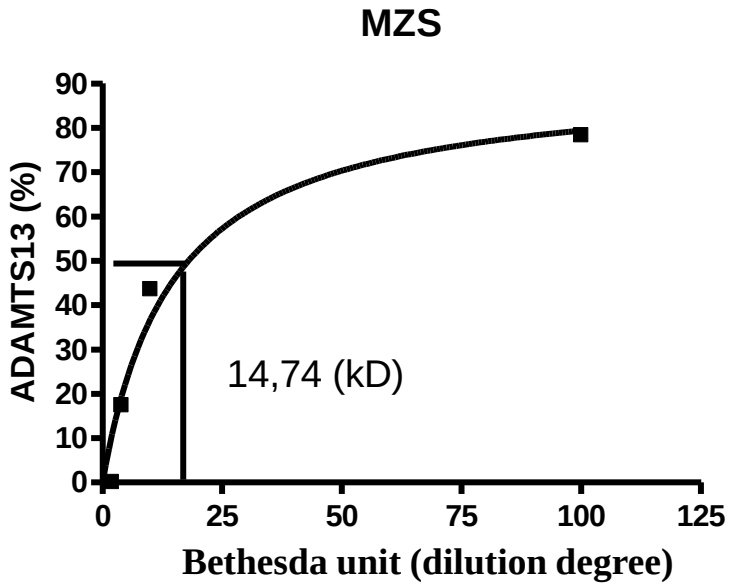


Madách K et al. Aneszteziológia és Intenzív Terápia, 2008; 38(1): 34-38

Functional measurement of inhibitory antibodies : Bethesda unit (BU)

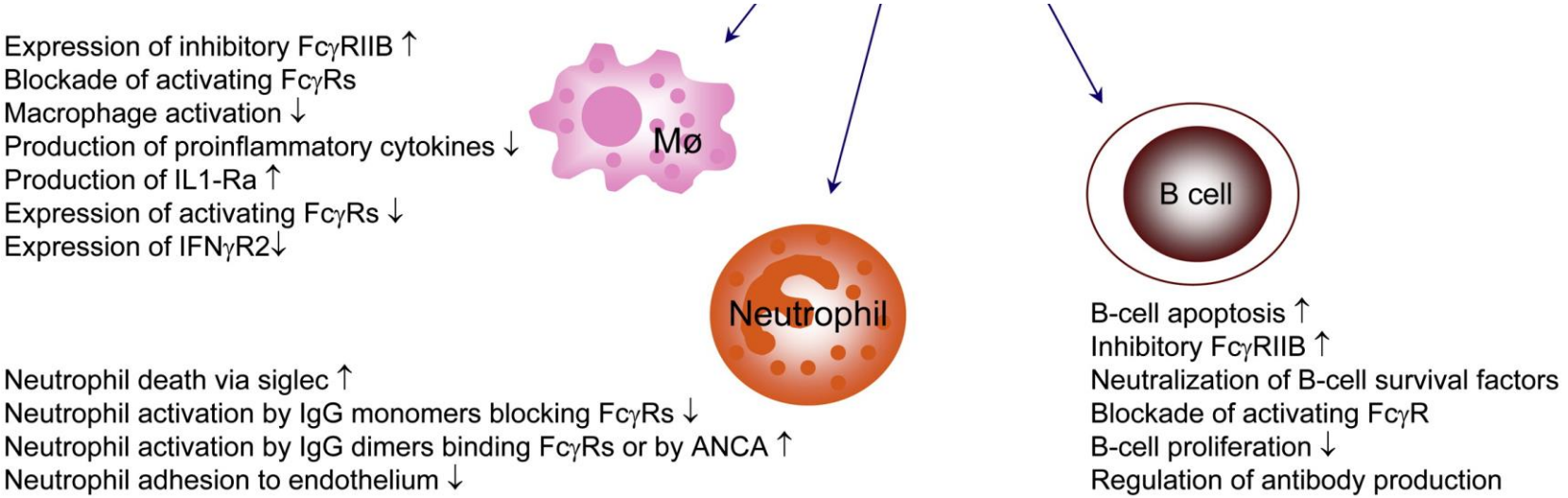
- The decreased activity plasma of the patient (0%) was mixed with increasing amount of 100% activity normal plasma, thus an increasing ADAMTS 13 activity could be measured
- If the activity of 1:2 rate mixed sample is 50%, then there is no inhibitory factor (=1 BU), the sample will simply dilute
- If the activity of the mixed sample is > 50% less than it would be expected from the mixture (e.g.<25% in this case), than presence of inhibitory factor is probable.
- Titration helps exact measurement



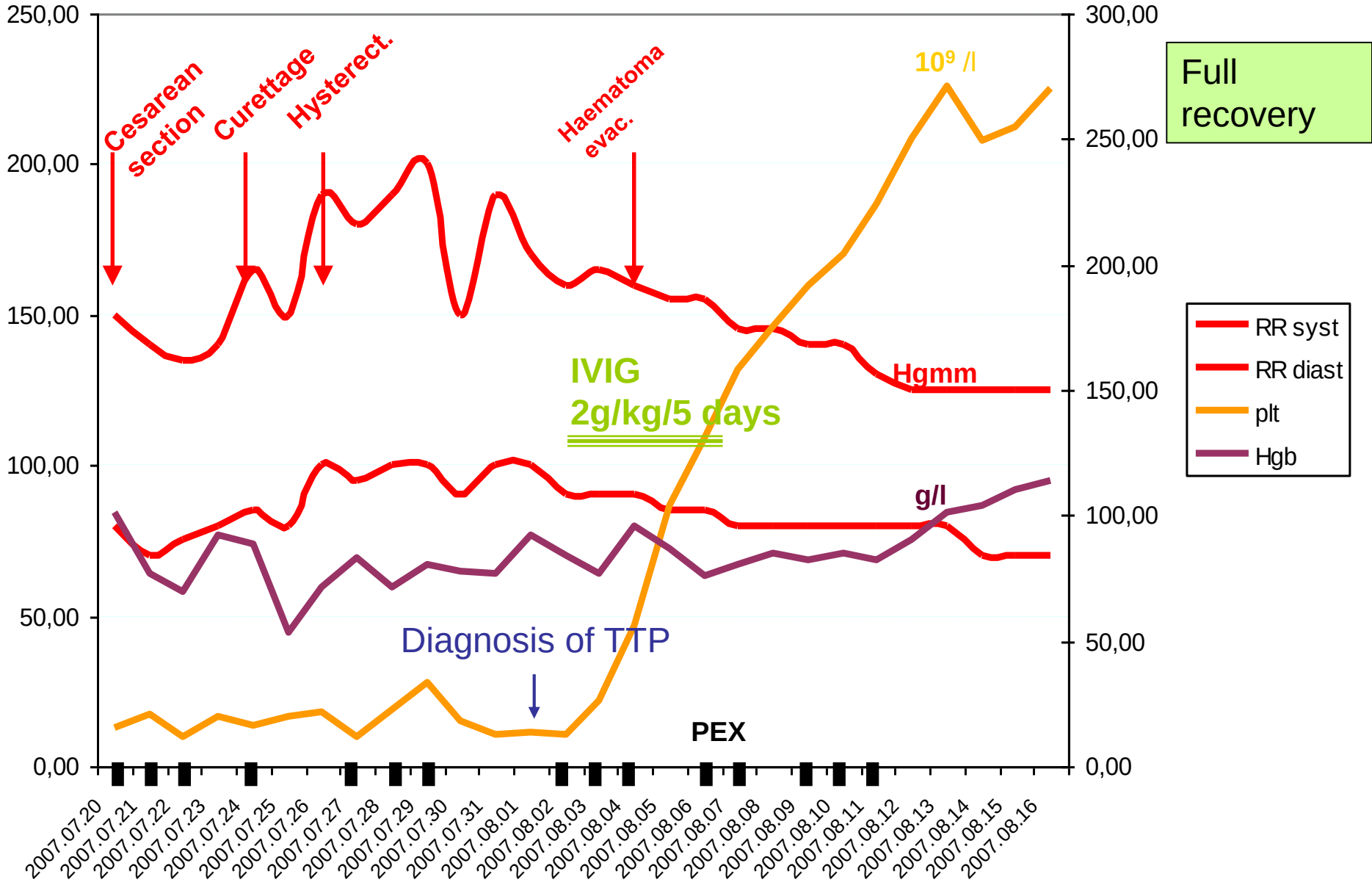


IVIG:

- Inhibition of anti-ADAMTS13 antibodies by infused anti-idiotype antibodies
- Acceleration of IgG catabolism
  - IVIG displaces the pathogenic antibodies from the endothelial FcRn receptors
- Acceleration of degradation of pathogenic antibodies
- Nonspecific inhibition of inflammatory response



Mechanisms of action of intravenous immune globulin *(IgIV)* on the immune modulation of various components of the innate and adaptive immune systems. (Adapted from Tha-In et al. Trend Immunol, 2008) *DC*, Dendritic cell; *Mo*, monocyte; *NK*, natural killer.



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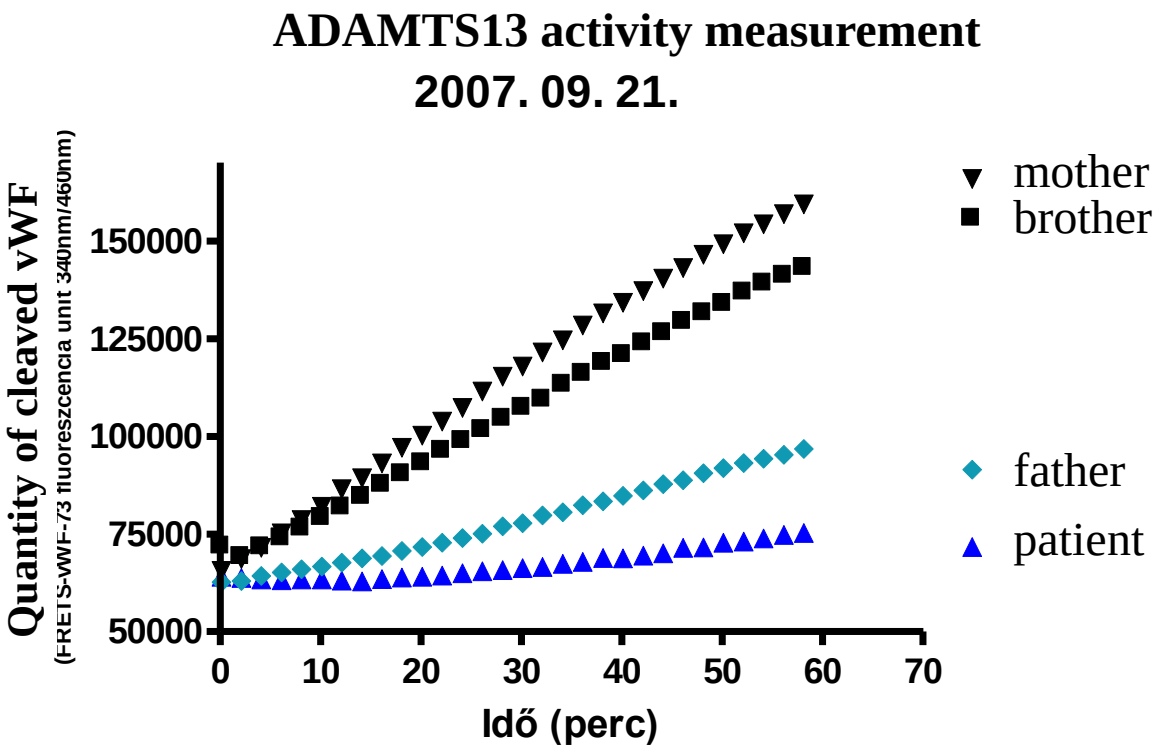
Treatment summary

- PEX: 17
- FFP: 17x6=102 U for PEX + 14 U FFP
- Matched rbc: 21 U
- Platelets: 22 U
- Humaglobin: 110 g
- Operations: 4 db
- Coronary plaques: a lot

Family screening

- Samples of the parents and one brother
- Decreased ADAMTS13 activity in the sample of the father (64%)



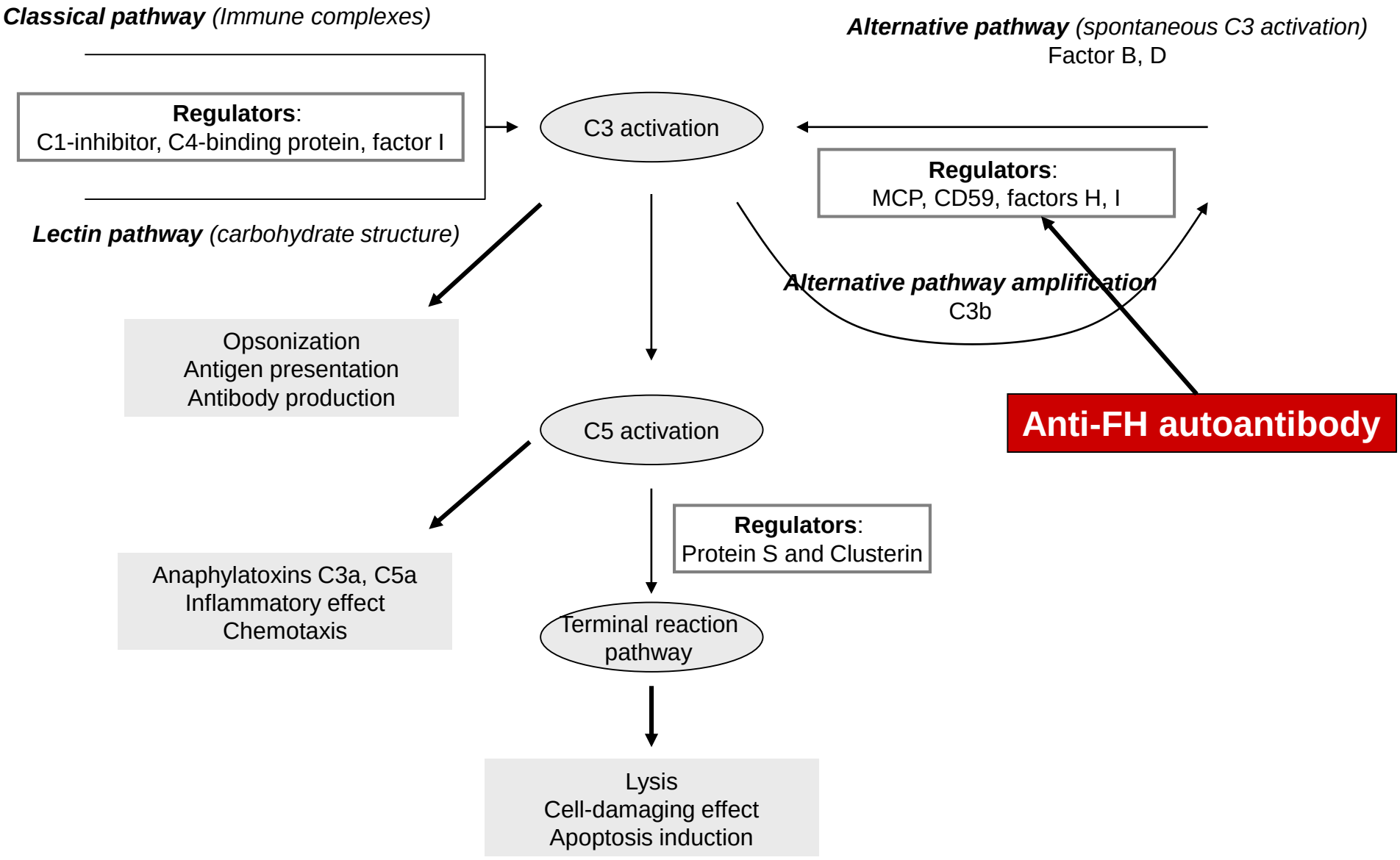
41 years old primipara

- Admission on the 38th week of an eventless pregnancy due to preeclampsia, suspected HELLP sy
- Caesarean section, living, mature 3500g girl
- Postoperative 12th hour:
  - Hb: 43 g/l, Plt: 40 G/l, AST: 1120 U/l, ALT: 932 U/l, LDH: 2937 U/l
  - creat 238umol/l, anuria, GFR↓
- Abrasion, PEX, steroid
  - Increasing inflammatory parameters, fever, debris in abrasion sample (G- rods)
  - DIC
- AB treatment, hysterectomy 24 hours after admission

Anti-FH autoantibody is positive: acquired, complement-mediated A-HUS is diagnosed

Dátum	Komment	Klasszikus út (48-103 CH50/mL)	C4 (0,15-0,55 g/L)	C3 (g/L); ref 0,9-1,8	Alternatív aktivitás WIE-ALT, %); ref 70-105	Anti-HF IgG (<110 AU/mL)	HF:Ag (mg/L); ref 127-447	I faktor, % (ref: 70-130)	B faktor, % (ref: 70-130)	ADAMTS13 aktivitás (67-147%)
2013.12.13	1. ferezis előtt	32	0,08	0,7	59	2797	208	86	69	28
2013.12.13	1- ferezis után	28	0,08	0,52	6	133	128	58	56	27
2013.12.16	3. ferezis után	40	0,18	0,44	16	41	189	89	52	29
2013.12.17	4. ferezis után	46	0,08	0,54	39	105	186	99	68	40
2013.12.19	5. ferezis után	35	0,13	0,61	54	34	164	119	71	53
2013.12.21	7. ferezis után			0,66	69	39	162	139	77	
2013.12.22				0,56	38	34	141	102	56	
2013.12.23				0,65	67	40	137	123	72	
2013.12.24				0,84	58	32	157	133	75	
2013.12.25				0,88	62	34	151	130	69	
2013.12.26				0,77	77	25	145	126	83	
2013.12.27				0,85	81	31	176	123	92	
2013.12.28				0,93	79	30	211	133	77	
2013.12.29				0,9	69	30	216	117	83	
2013.12.30				1	82	25	214	108	75	
2013.12.31				1,01		47	301			37
2014.01.01				1,17			289			

Outline of functioning of the complement system



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  - Drug-mediated (toxic dose)
    - Removal of drug, supportive
  - **Complement-mediated (A-HUS)**
    - **PEX, immunosuppression, anticomplement agent**

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Therapeutic possibilities of aHUS

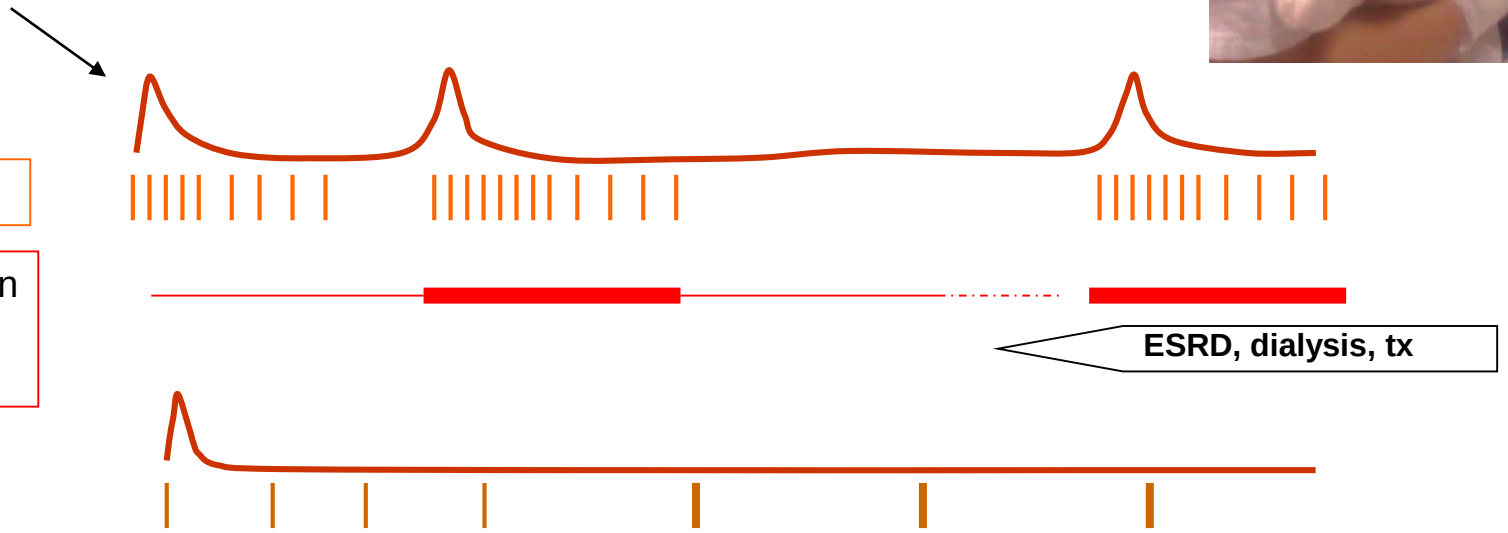
MODS: liver, kidney (HD), respiration (NIV), haemostasis, 6x parenteral antihypertensive treatment.

The illness is characterized by recurrent exacerbations
(hemolysis, fragmentocytes, ↑LDH, ↓plt)

Therapy:

PEX

Immune suppression
Cytostatic drugs
Rituximab

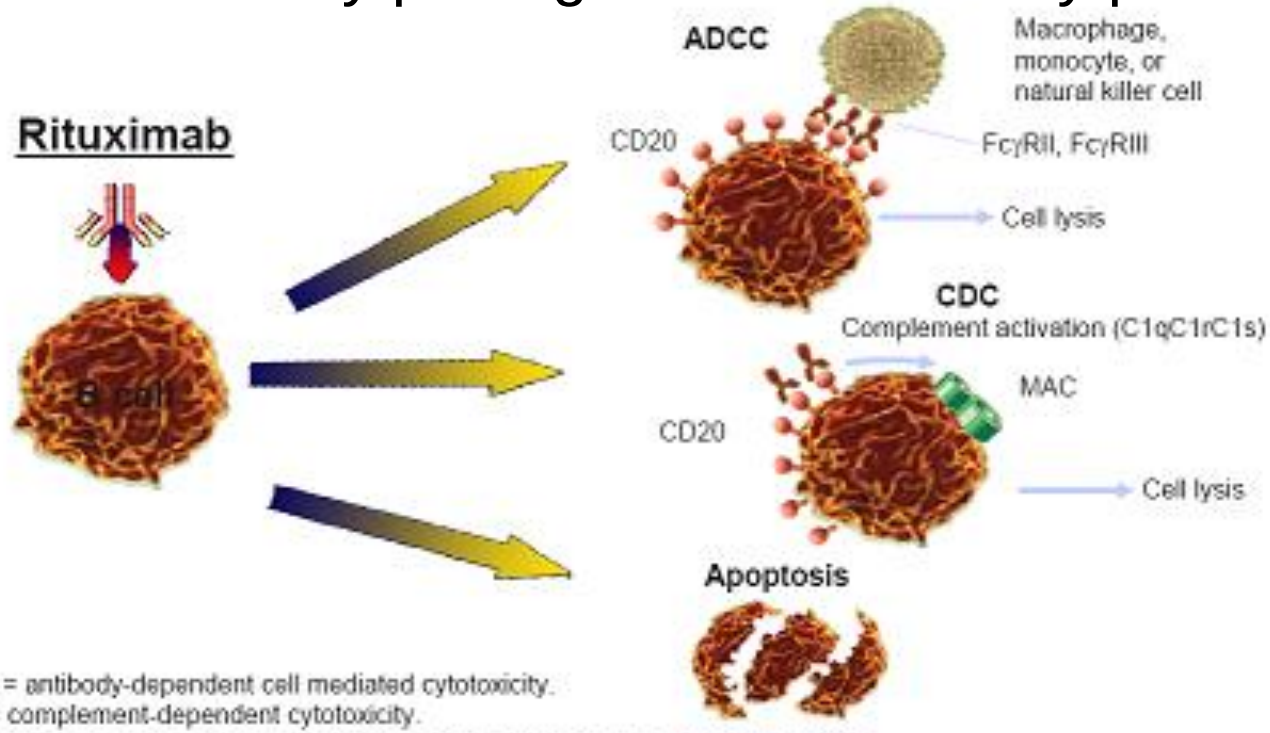


Anticomplement
Eculizumab
900 mg/week for 4 weeks,
then 1200 mg/two weeks

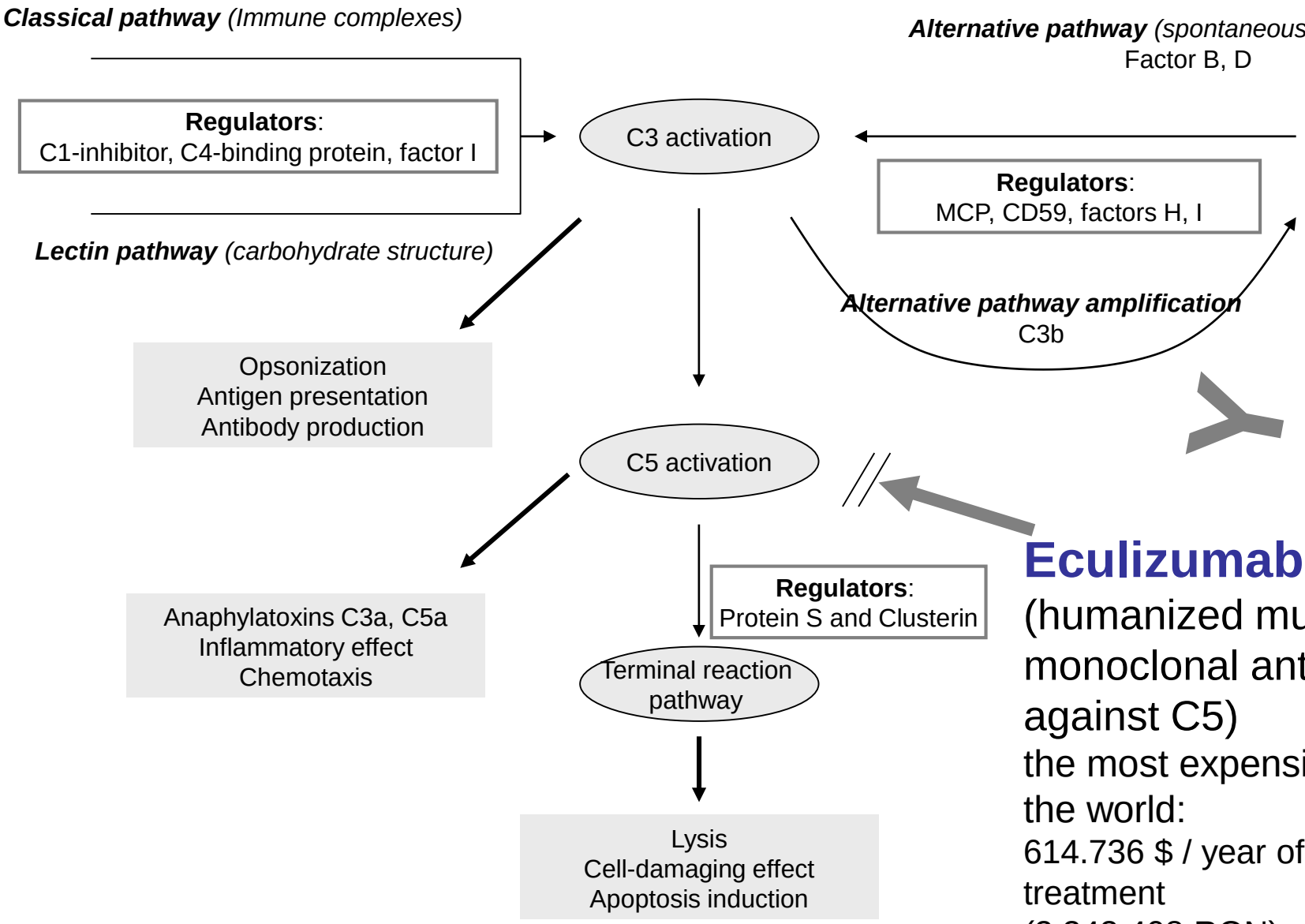
With the consent of Prof. Zoltán Prohászka

Rituximab (Rituxan, MabThera)

- is a chimeric monoclonal antibody against the protein CD20, which is primarily found on the surface of B cells. Rituximab destroys B cells and is used to treat diseases which are characterized by excessive numbers of B cells, overactive B cells, or dysfunctional B cells.
- The goal is to destroy pathogenic autoantibody producing B cells



Targeted inhibition of pathologic complement activation



Eculizumab
(humanized murine monoclonal antibody against C5)
the most expensive drug in the world:
614.736 $ / year of ongoing treatment
(2.343.408 RON)

Therapy-outcome

- IVIG ineffective
- For this reason there is no point in trying Rituximab
- Cyclophosphamid ?
- Eculizumab? Targeted therapy, but the most expensive drug of the world
- Application for approval of financial guarantee to the National Health Insurance Fund- very complex administration
- „Kidney transplantation is cheaper”


PME
Dive in
34
Thought leadership
Appointments
Regulatory
Healthcare
UK's 'Promising Innovative Medicine
03 September 2014
NICE draft guidance recommends eculizumab (Soliris) for treatment of very rare life-threatening blood disorder
Eculizumab (Soliris, Alexion), a drug to treat a very rare blood disorder affecting around 200 people in England, has been recommended by NICE in further draft guidance.
A drug to treat a very rare blood disorder affecting around 200 people in England has been recommended by the National Institute for Health and Care Excellence
Share
Print
Eculizumab radically improves the quality of life of the small number of people with aHUS.
NICE Chief Executive Sir Andrew Dillon
NICE National Institute

Therapy-outcome

- Full recovery with IVIG, PEX and steroid! (?)
  - Permanently negative anti-FH level
  - Resolving complement profile and normal FH, C3 levels
  - Kidney function goes back to normal within 6 weeks
- Examination of the samples from the newborn did not show transplacental transport of anti FH autoantibodies, normal complement profile was detected.
- Either the patient does not know the textbook, or the textbook does not know the disease

Do we just over/look or actually can see the disease?

- HELLP definition 1982
- Thrombotic thrombocytopenic purpura (TTP)
  - Disease 1924
  - ADAMTS13 deficiency 1982
  - PEX efficiency 1991
- Haemolytic uraemic syndrome (HUS)
  - Disease 1975
  - Enhanced complement activation 1998
  - Complement factor H autoantibodies 2005
  - Rituximab 2007, Eculizumab (FDA, EMA) 2011

Summary

- Mortality of HELLP sy. can be as high as 86%, but in this case role of TMA should be considered
- If there is no improvement within 48h with PEX, TMA should be considered
- Extensive laboratory diagnostics and close monitoring of trends is needed, the clinical picture is insufficient on its own.
- Many types of TMA became treatable with targeted therapies (not jut with steroids, cytostatic drugs)
- Possibilities: substitution, non-specific inhibition, targeted inhibition

I can do things you cannot,

You can do things I cannot,

Together we can do great things!

Mother Teresa