Atypisch hemolytisch uremisch syndroom

aHUS

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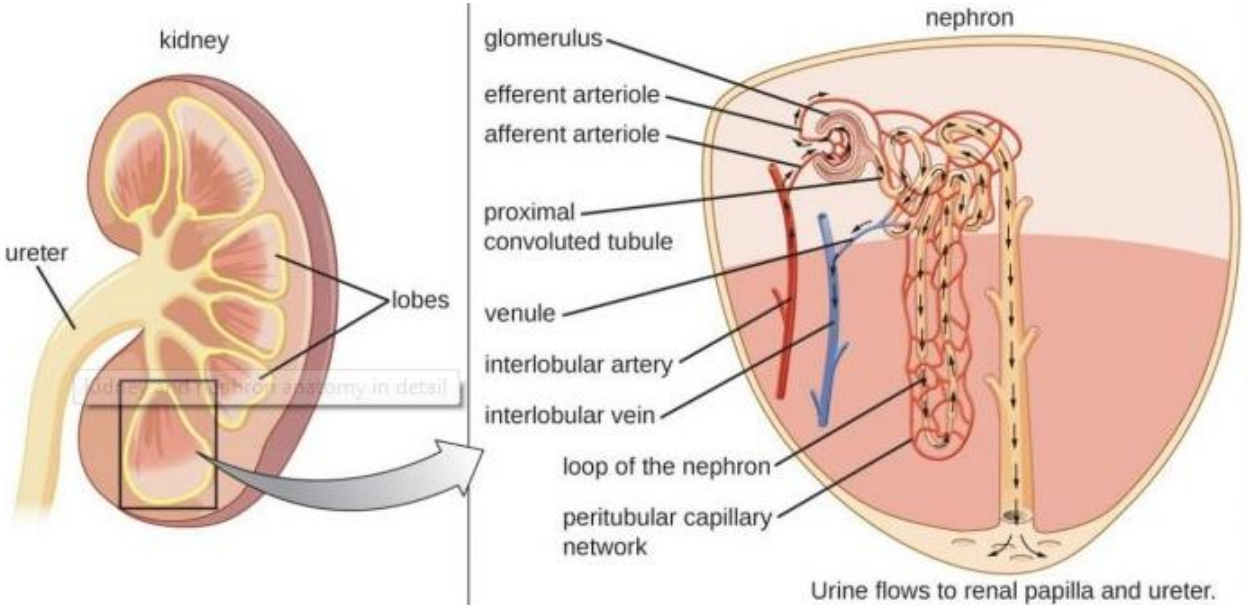
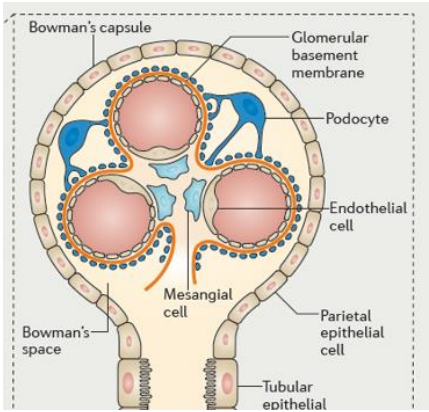
Hemolytisch uremisch syndroom

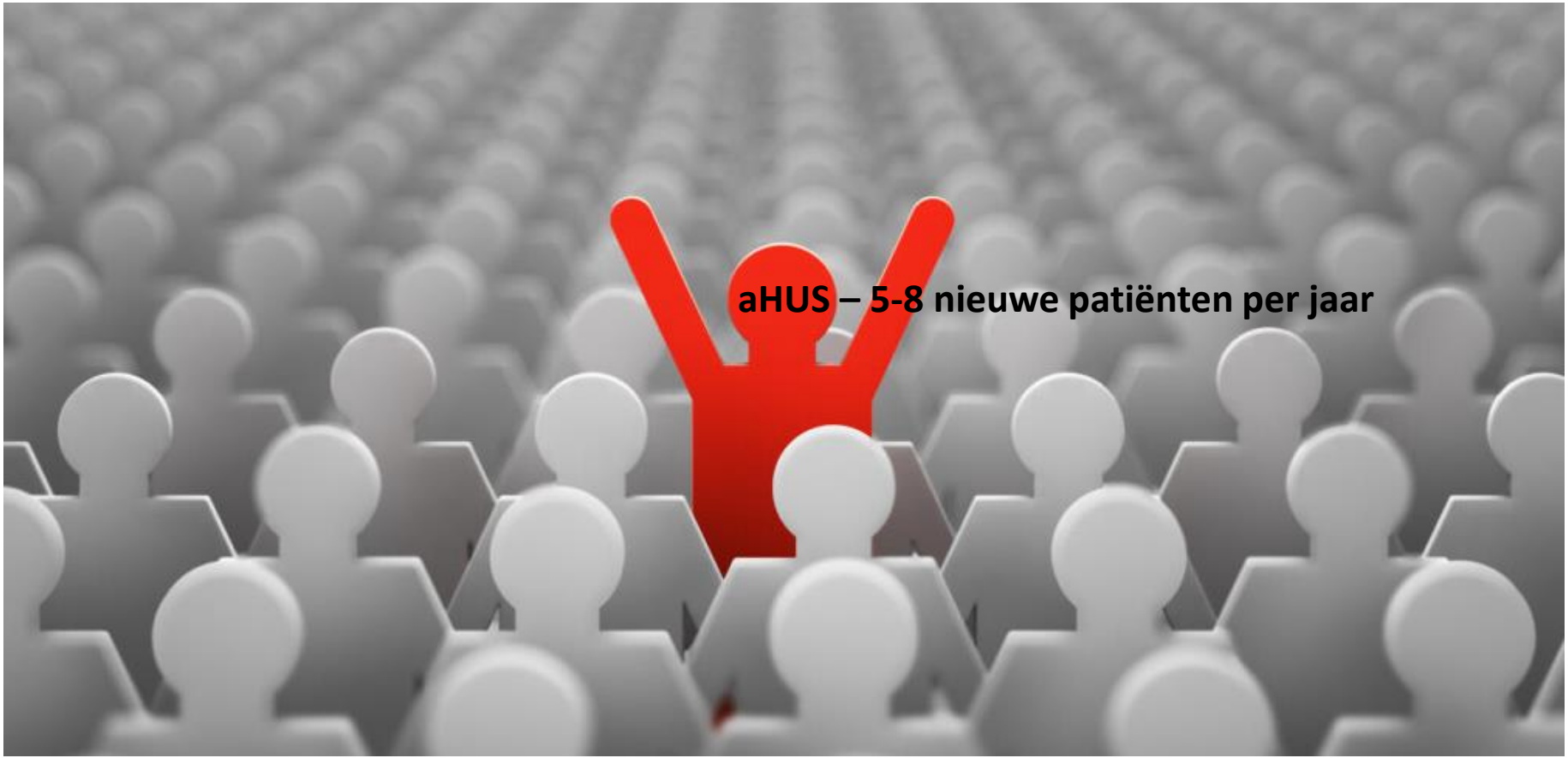
- Versnelde afbraak van rode bloedcellen = hemolyse
- Tekort aan bloedplaatjes in bloed
- Slechte nierfunctie – acuut nierfalen = uremie

- Stolsels / kleine bloedpropjes in de bloedvaatjes van de nier = thrombotische micro-angiopathie (TMA)

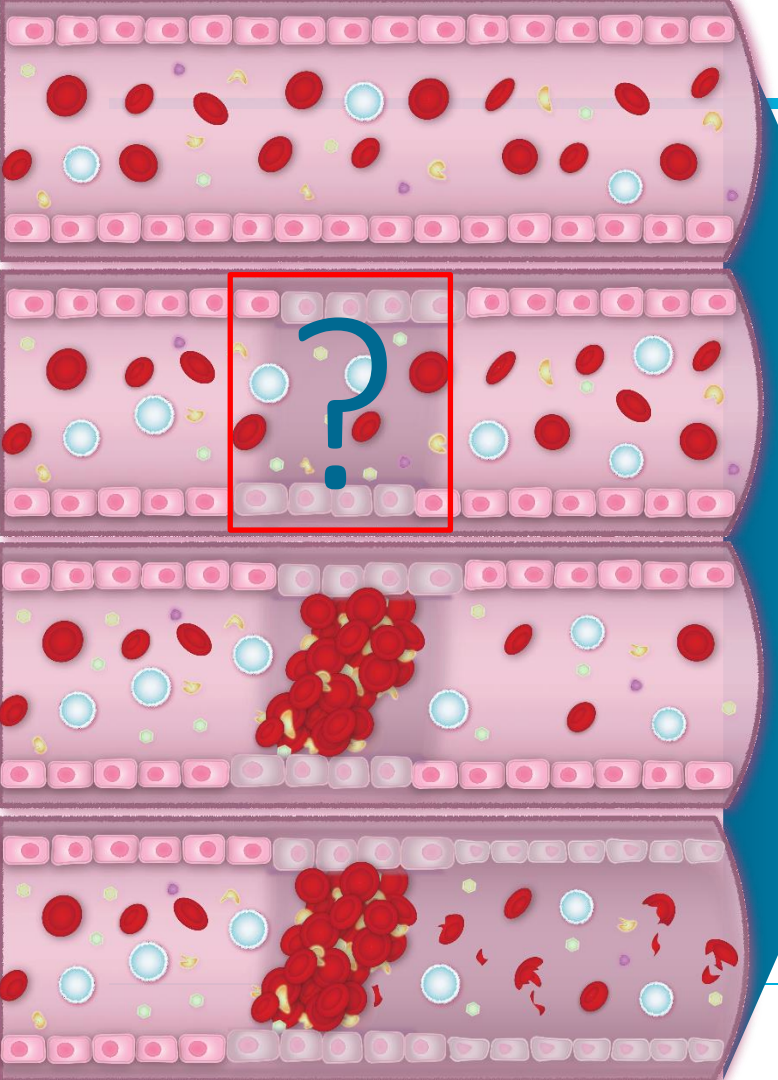
Nier – Zuiverings-eenheid - glomerulus

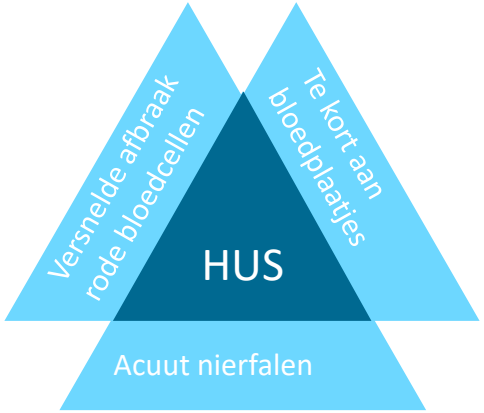


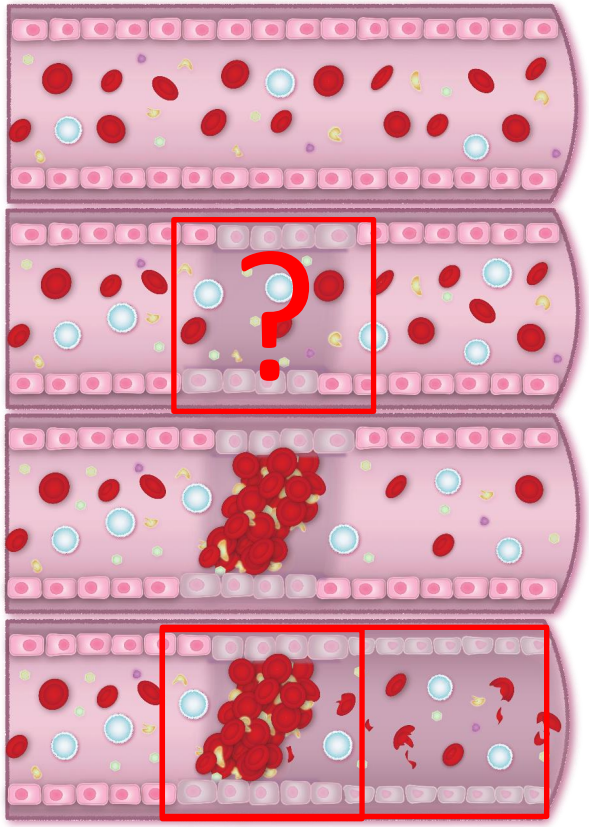



aHUS – 5-8 nieuwe patiënten per jaar


aHUS – 5-8 nieuwe patiënten per jaar
Diabetes mellitus – 50.000 nieuwe patiënten per jaar


?


Versnelde afbraak rode bloedcellen
Te kort aan bloedplaatjes
HUS
Acuut nierfalen



Hemoglobine ↓
Thrombocyten ↓
LDH ↑
Haptoglobin ↓
Schistocytes ↑

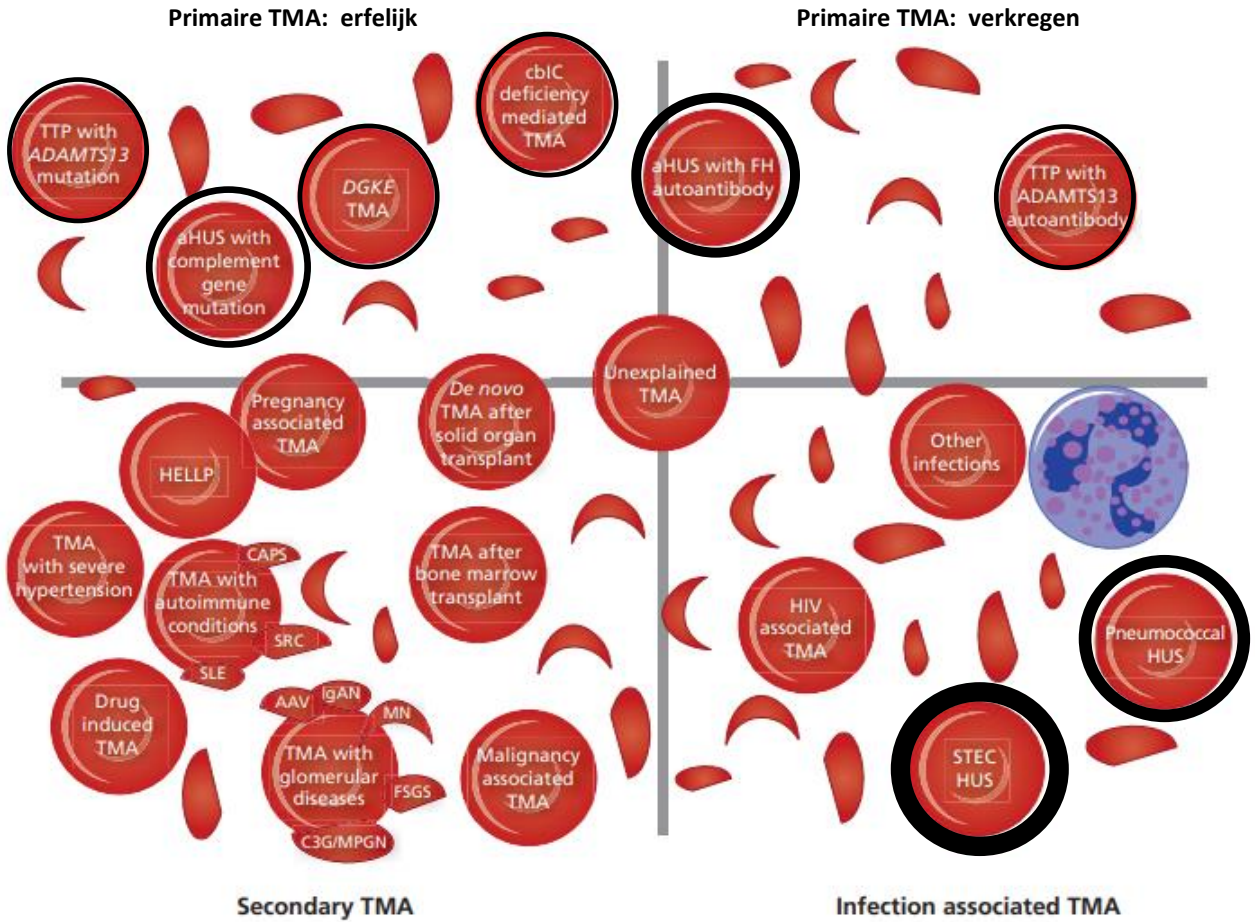
Hemolytische Anemie Thrombocytopenie

Thrombotische Microangiopathie

Kreatinine ↑
Ureum ↑

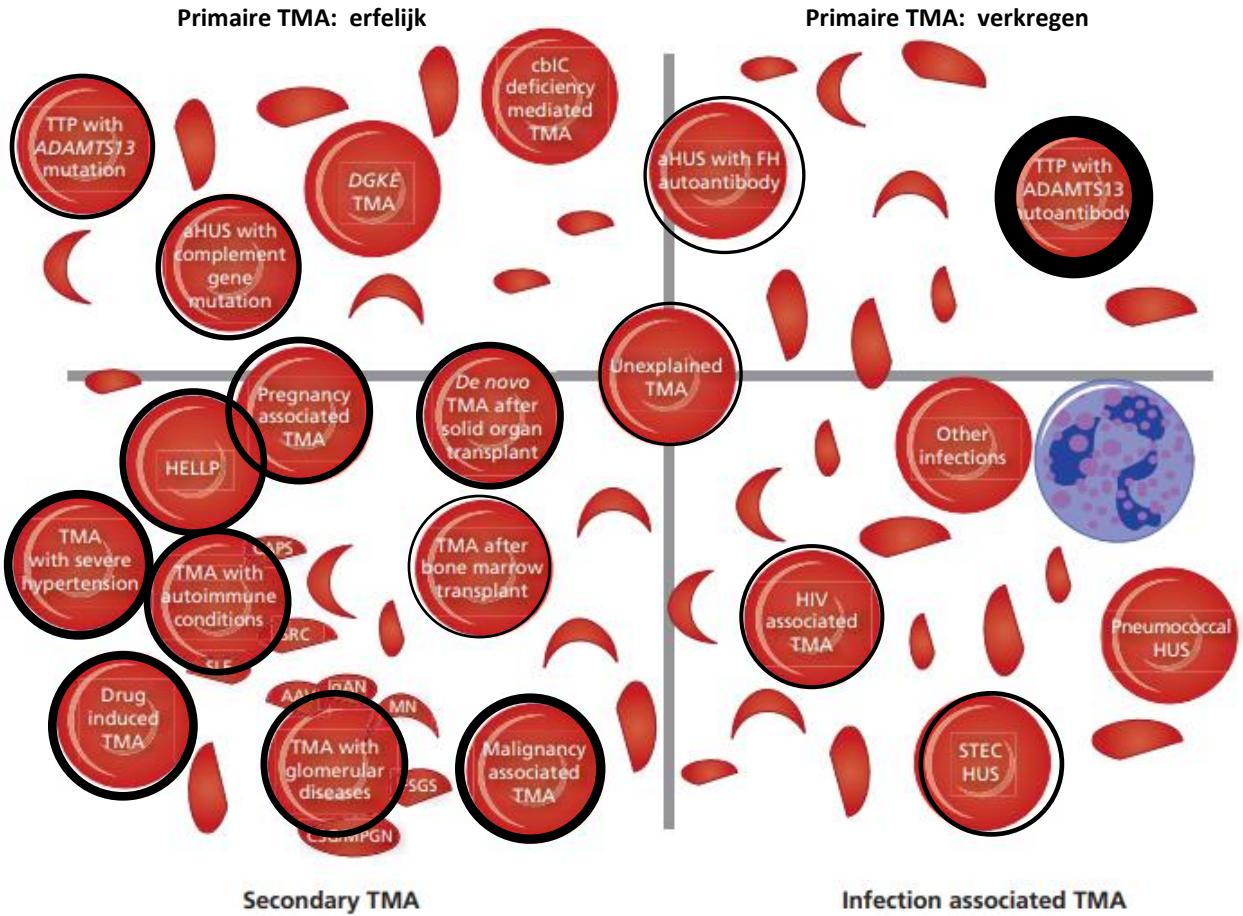
Acuut nierfalen

Hemolytisch Uremisch Syndroom



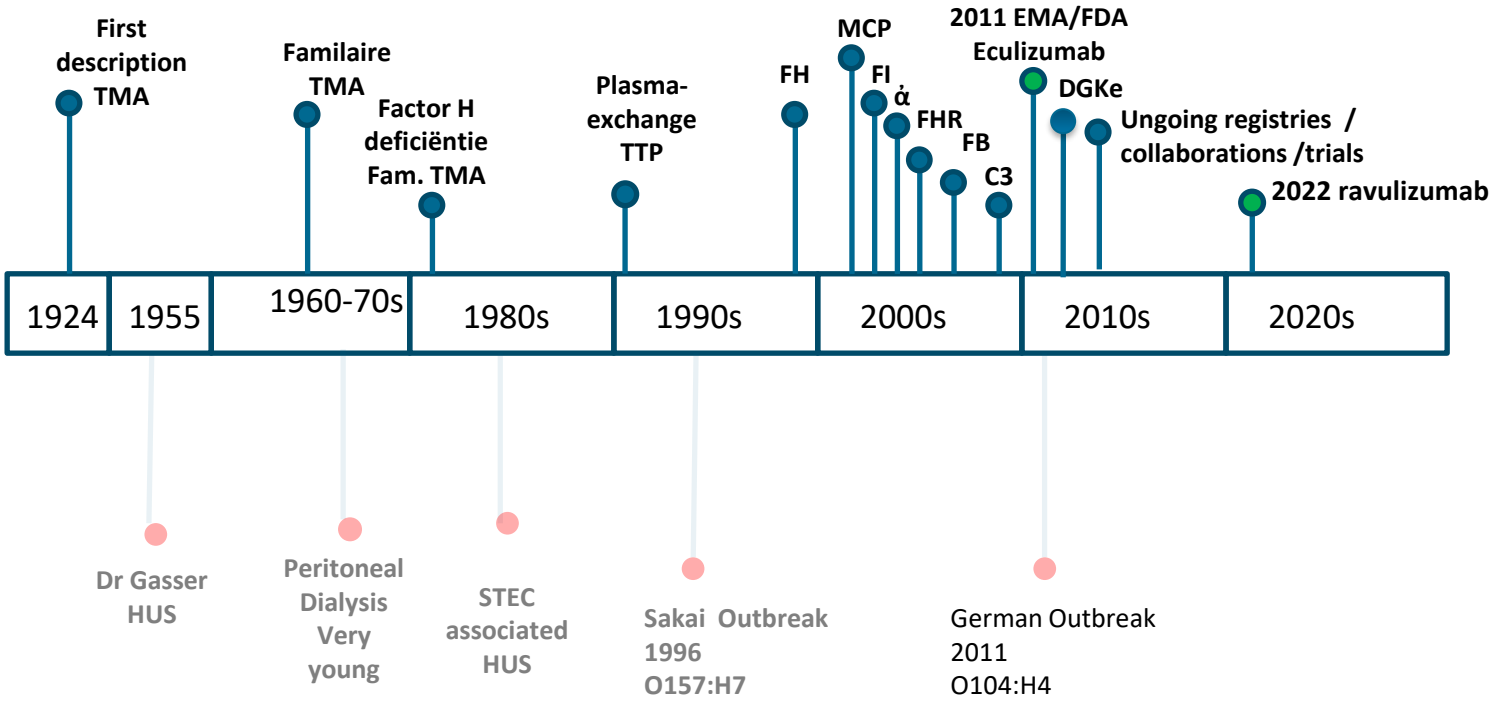
Children

Brocklebank et al, CJASN 2018

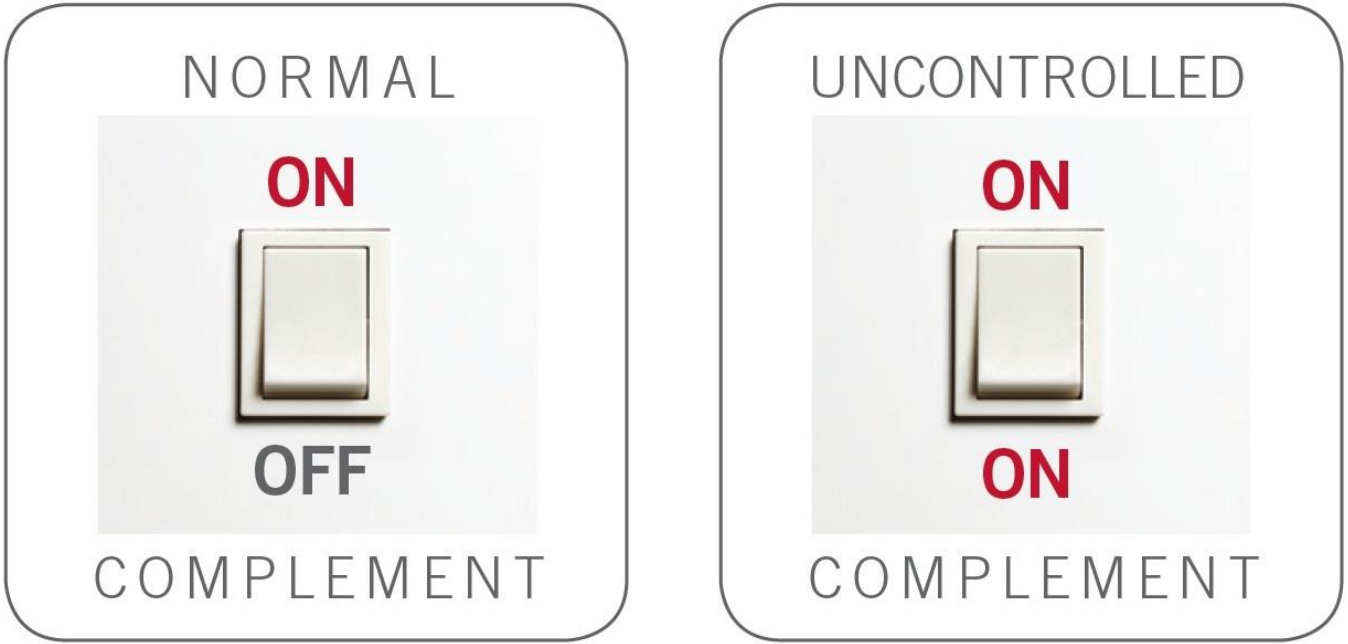


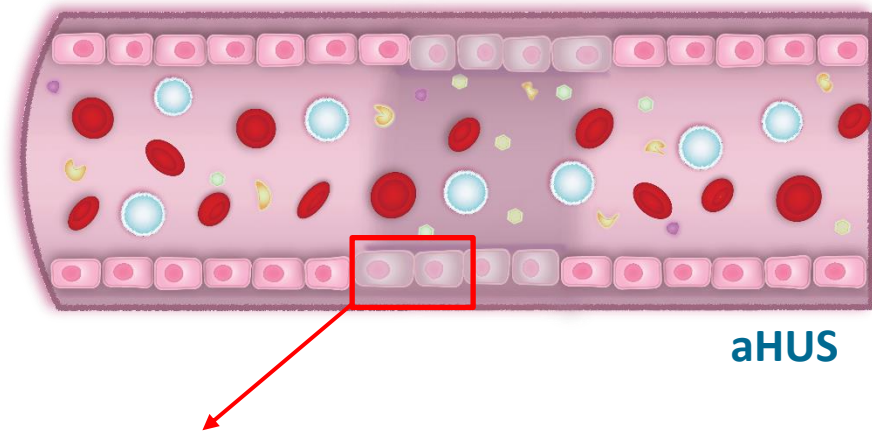
volwassenen

Brocklebank et al, CJASN 2018


First description TMA
Familaire TMA
Factor H deficiëntie Fam. TMA
Plasma-exchange TTP
FH
MCP
FI
ά
FHR
FB
C3
2011 EMA/FDA Eculizumab
DGKe
Ungoing registries / collaborations /trials
2022 ravulizumab
1924
1955
1960-70s
1980s
1990s
2000s
2010s
2020s
Dr Gasser HUS
Peritoneal Dialysis Very young
STEC associated HUS
Sakai Outbreak 1996 O157:H7
German Outbreak 2011 O104:H4

Atypische HUS (aHUS)




aHUS
Complement

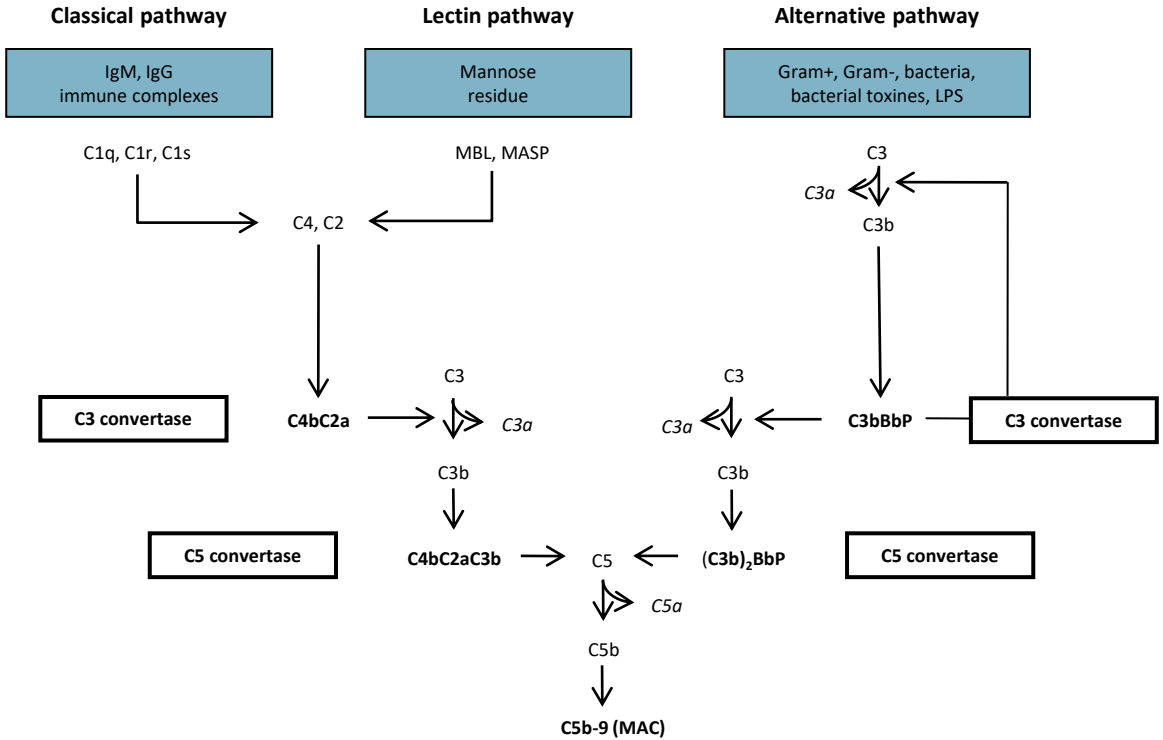
- Atypische hemolytisch uremisch syndroom (aHUS)

- **Complement gemedieerde atypisch hemolytisch uremisch syndroom (CaHUS)**

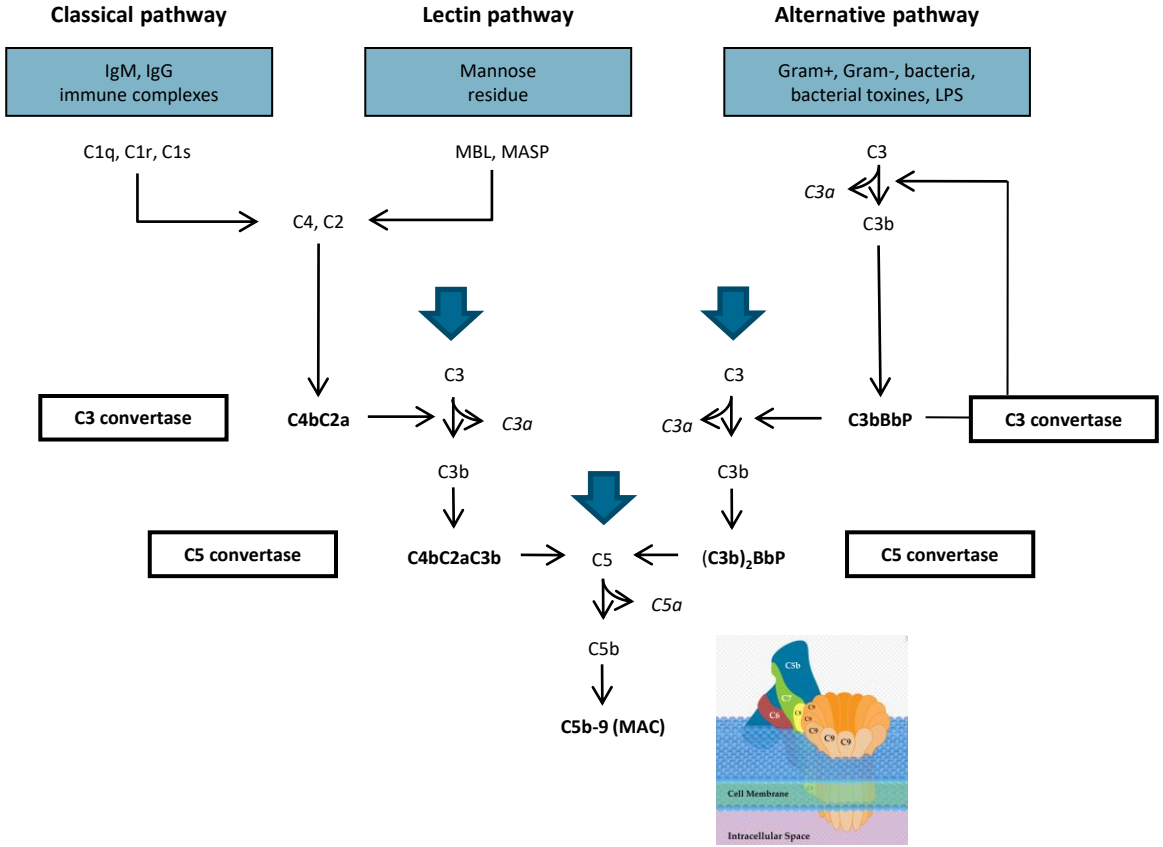
Het complement systeem

- Onderdeel van het menselijke afweer systeem
- In de evolutie al zeer lang aanwezig en bij vele diersoorten , evenals de mens
- Groep van eiwitten (30-40) die elkaar in een kettingreactie in gang zetten om uiteindelijk een bacterie / virus onschadelijk te maken of oude cellen /materiaal op te ruimen
- 3 routes van kettingreacties mogelijk

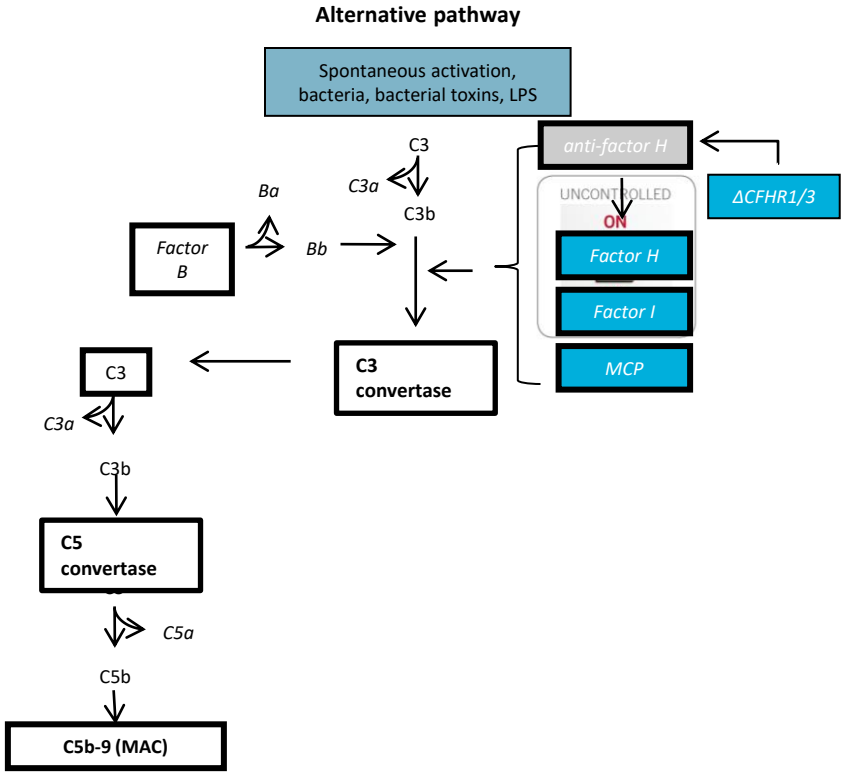
Het complement systeem

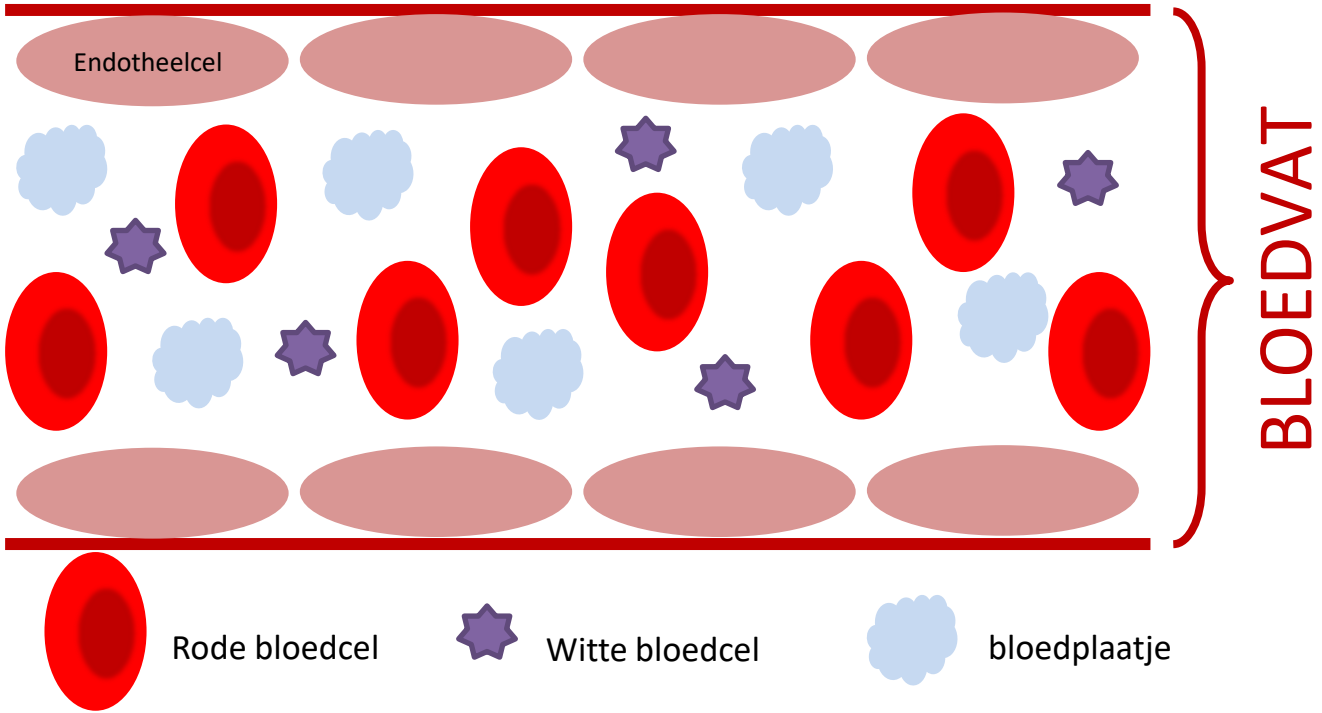


Het complement systeem

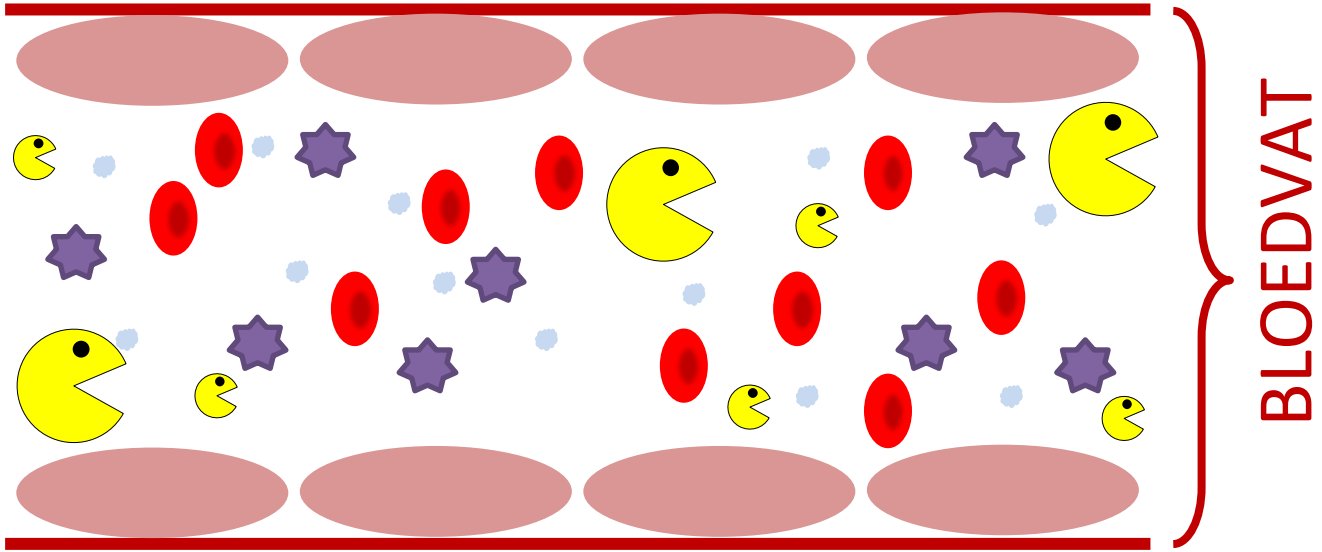


Regulatoren van de 3e route

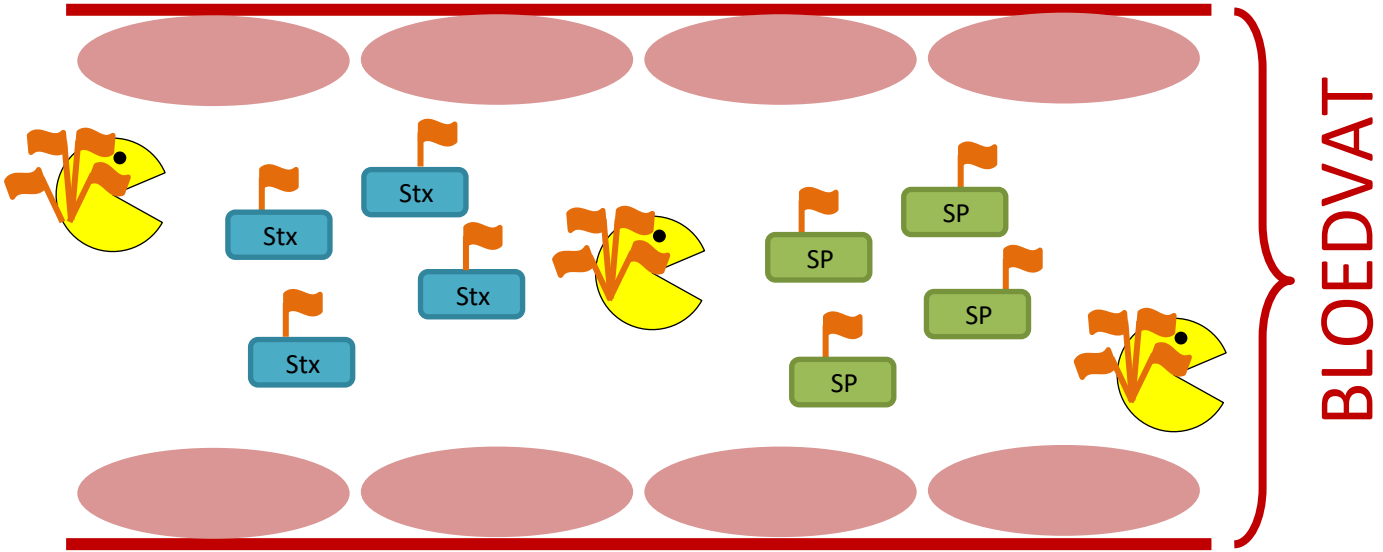



Endotheelcel
BLOEDVAT
Rode bloedcel
Witte bloedcel
bloedplaatje

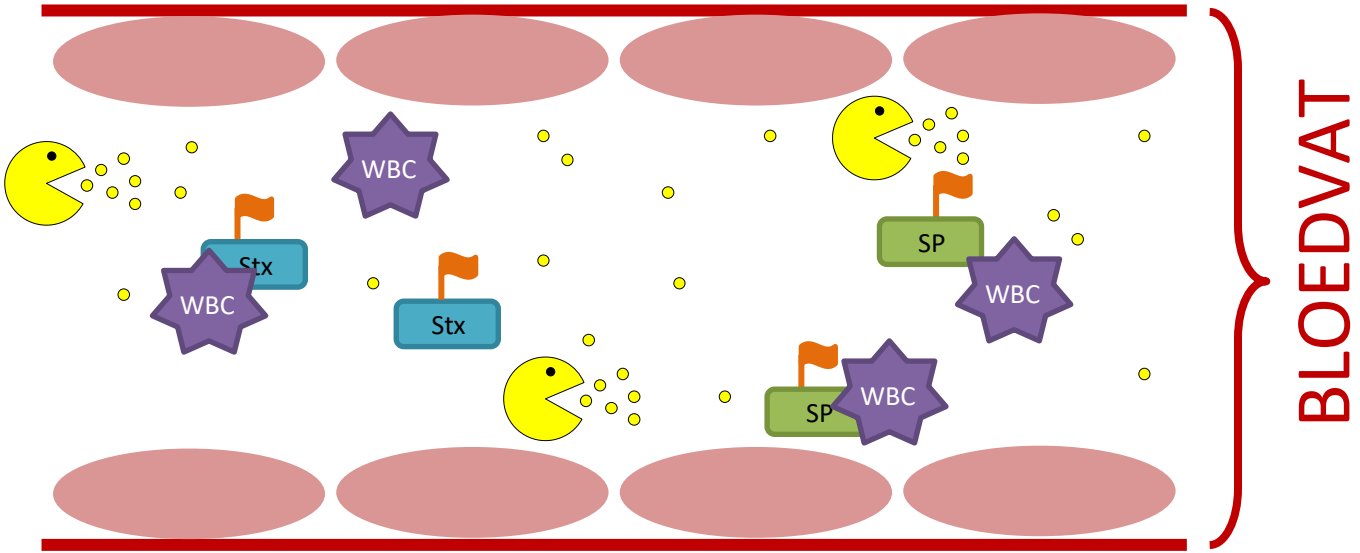
Complementsysteem



Complementsysteem en indringers

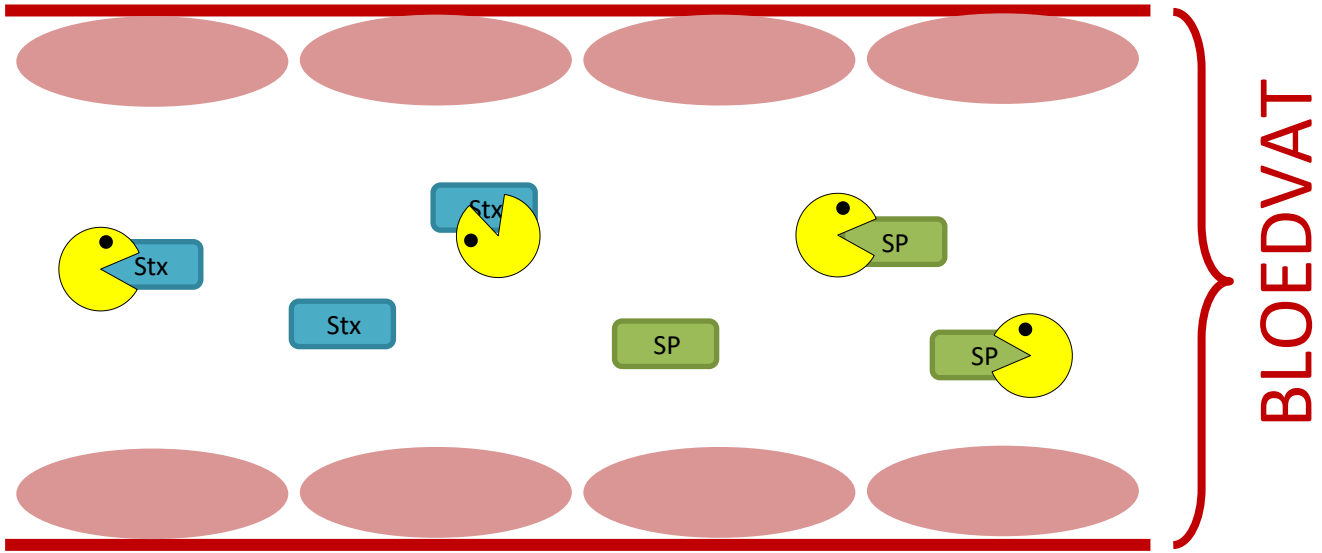


Complementsysteem en indringers

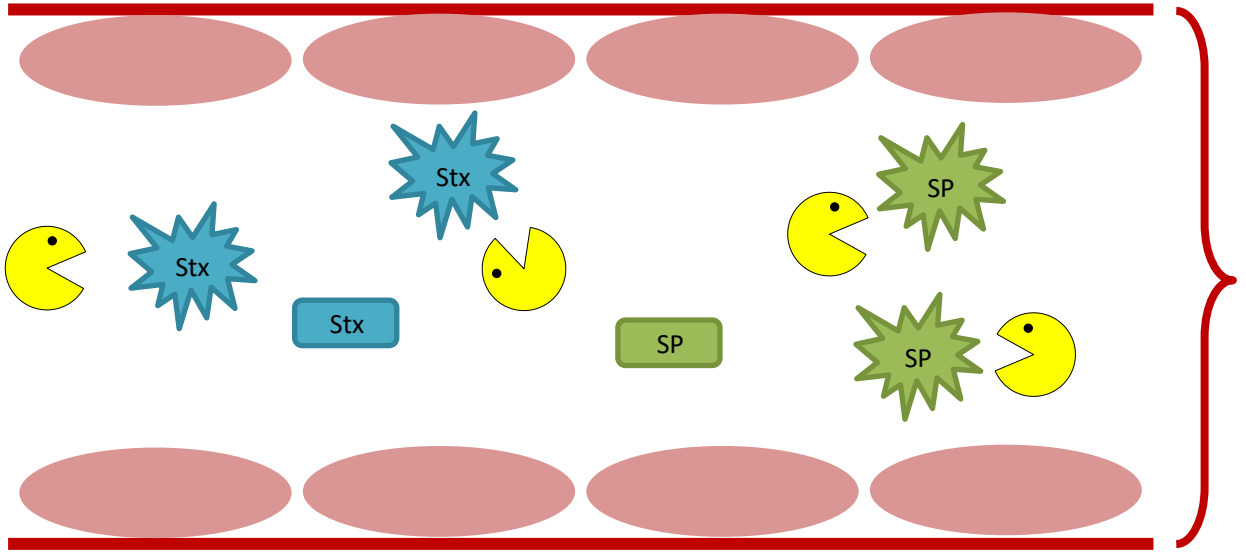


- Aantrekken van witte bloedlichaampjes om indringers op te ruimen.

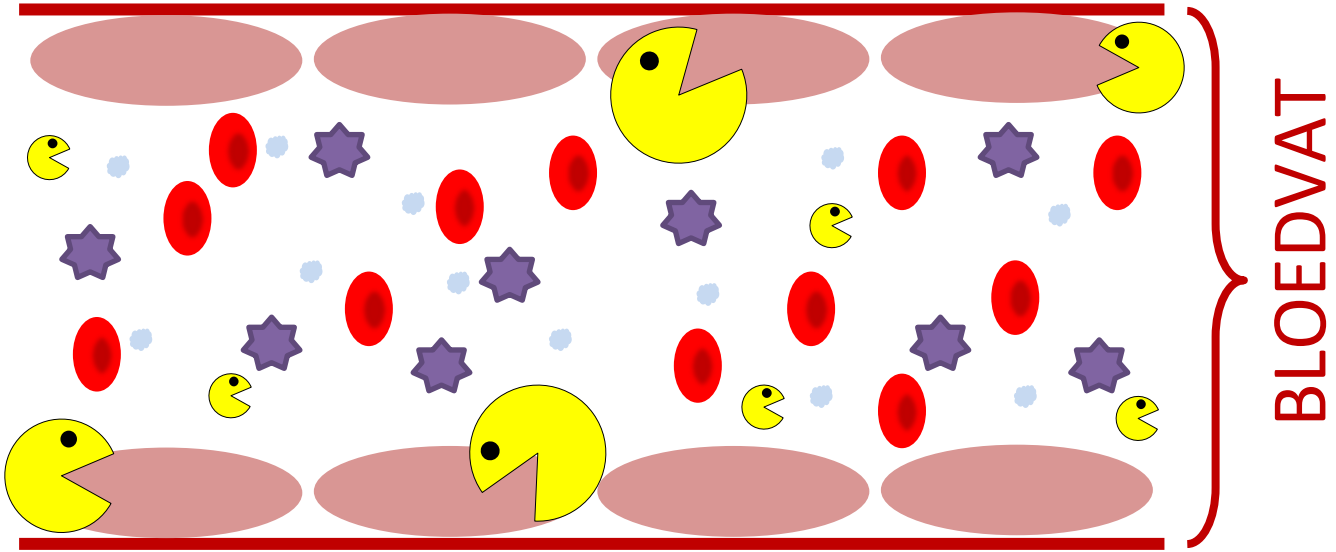
Complementsysteem en indringers



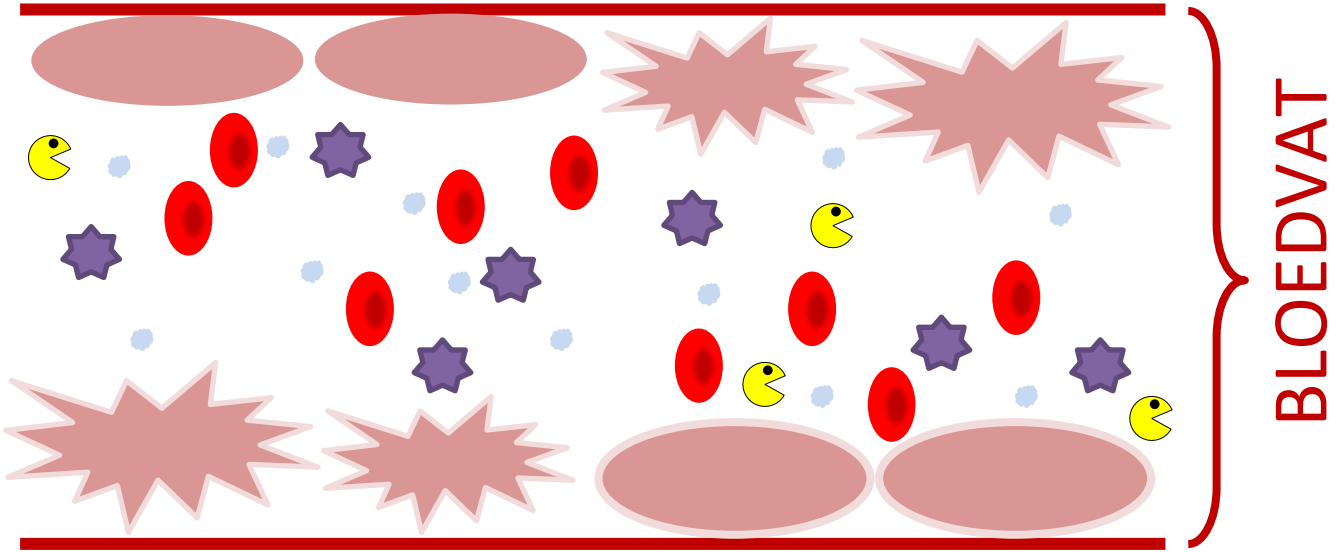
Complementsysteem en indringers



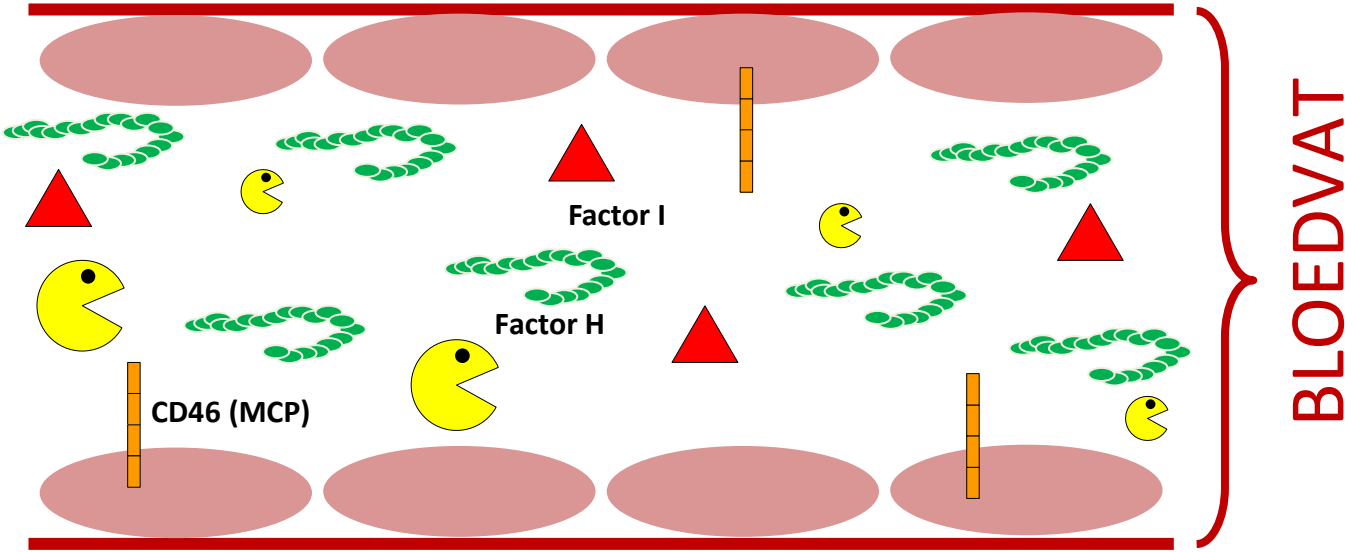
Complementsysteem en eigen cellen



Complementsysteem en eigen cellen



Regulatie van het complementsysteem



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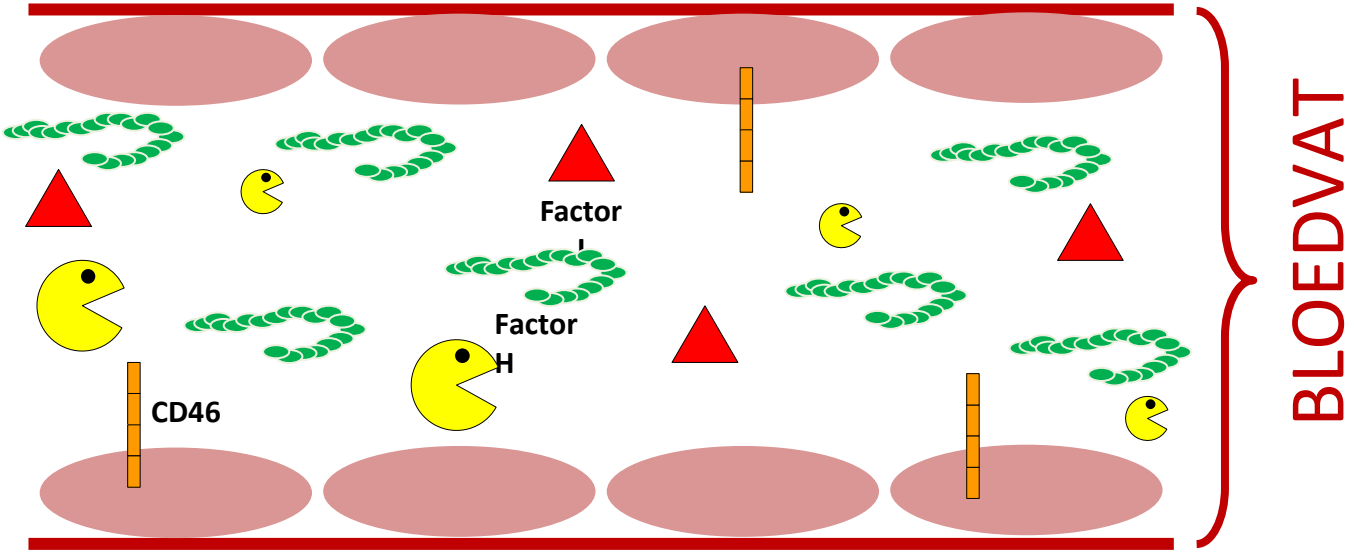
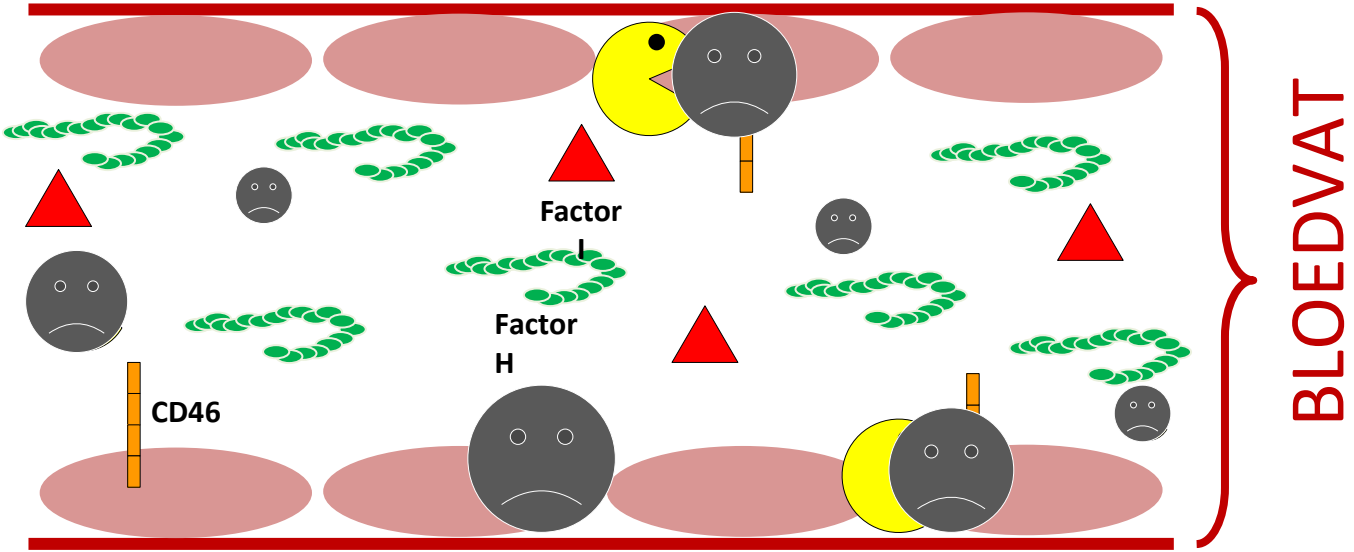


Regulatie van het complementsysteem



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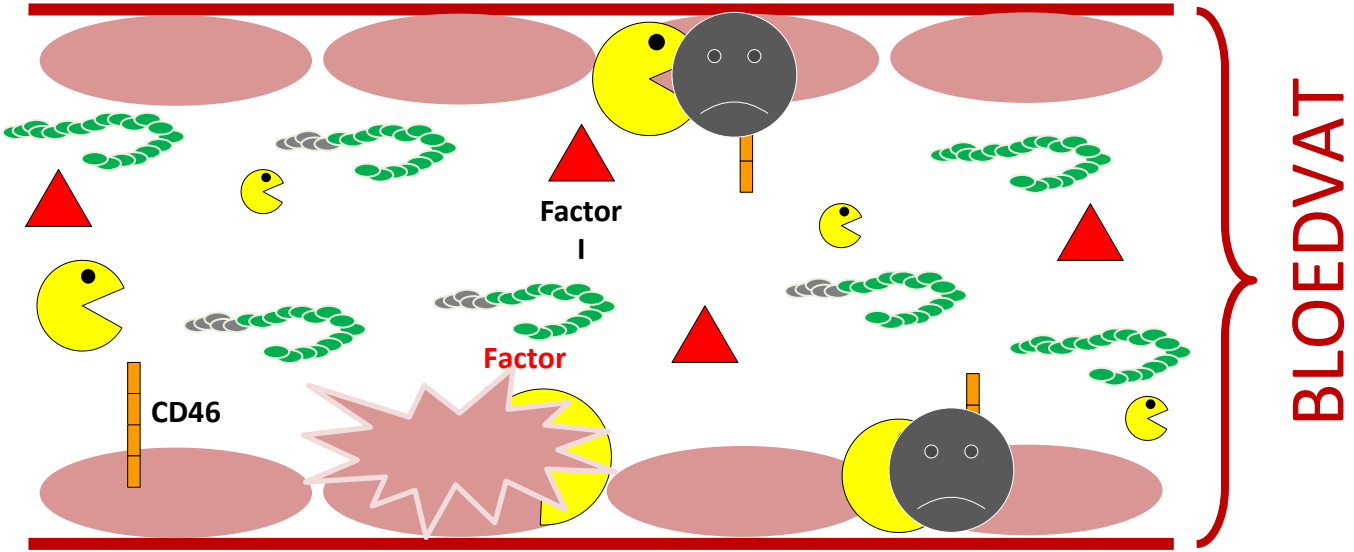
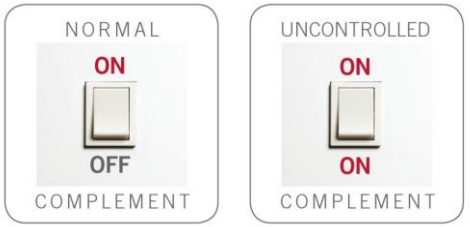


Hoe ontstaat aHUS



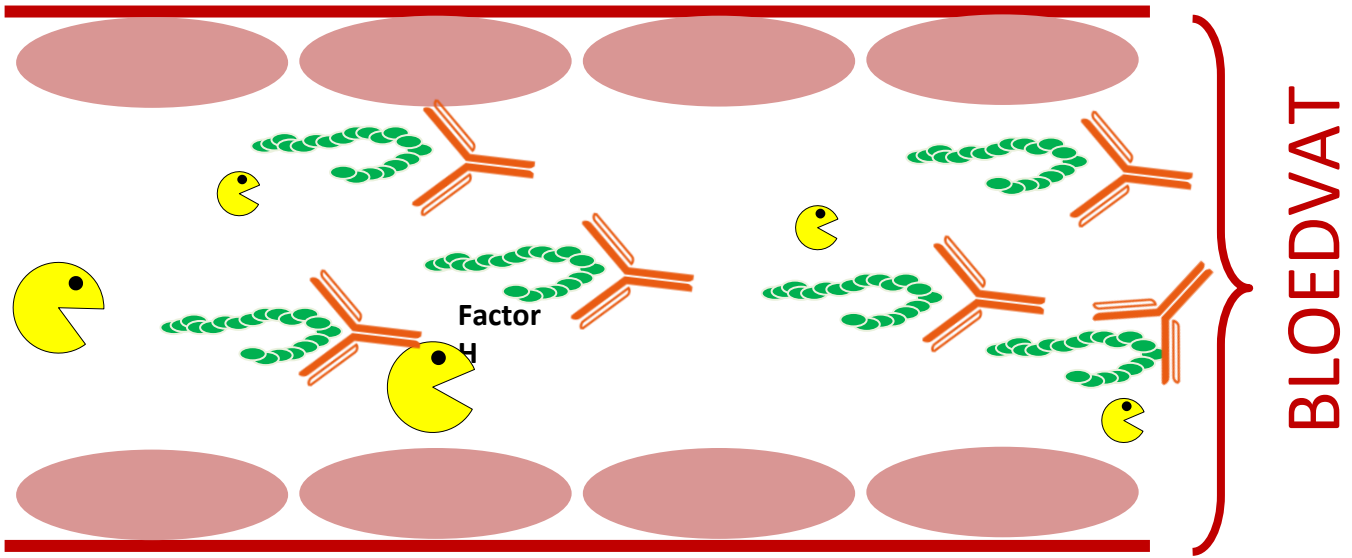
- <u>Dysregulatie/ overactivatie complement</u>

- Verschillende oorzaken dysregulatie:
  - Vaak extra factor/prikkel nodig zoals infectie : bacteriën, virussen

  In combinatie met
  - Verandering in erfelijke code van een van de complement eiwitten
  - Auto-antistoffen tegen complement eiwit

- Normaal : inactiveren van systeem door specifieke eiwitten = regulatoren

Antistoffen tegen factor H zorgen dat factor H niet aan de vaatwand kan binden en zo dus de vaatwand niet beschermd wordt tegen complement activatie



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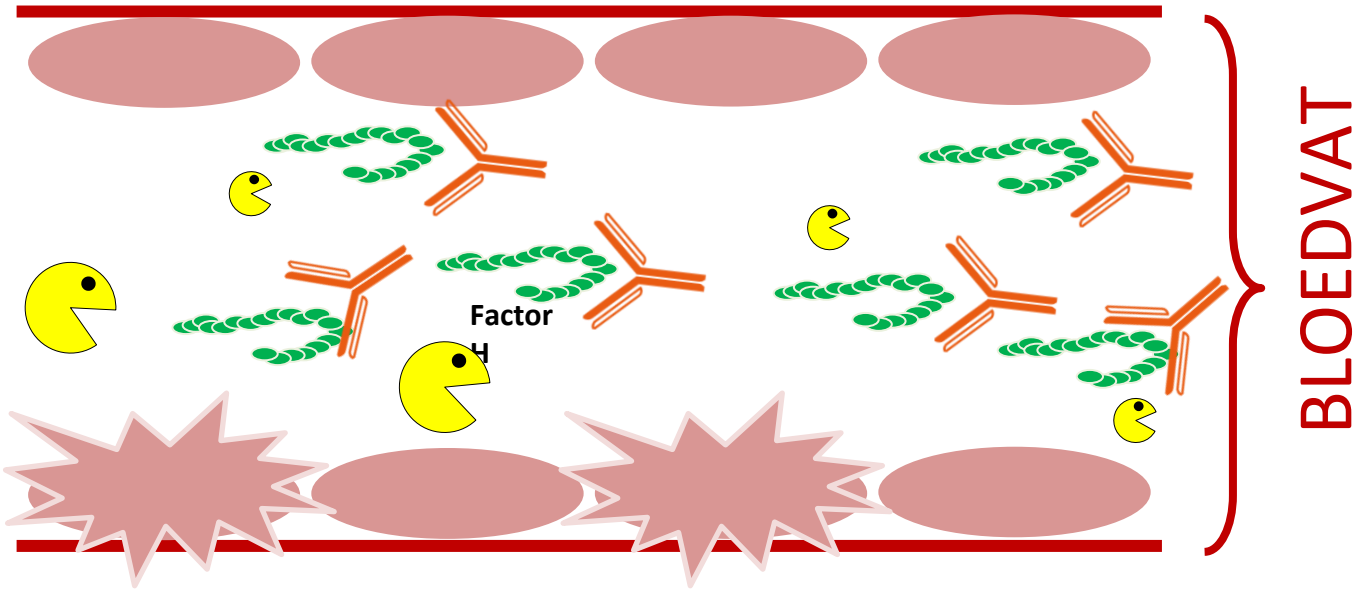
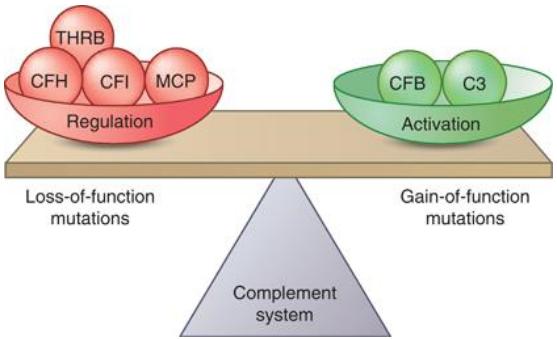
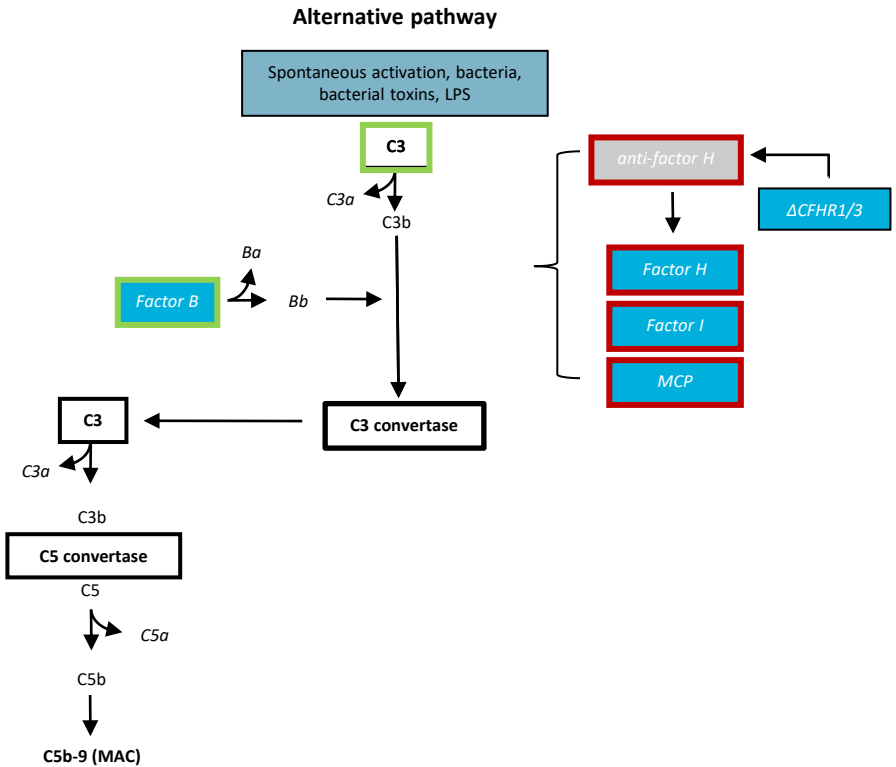
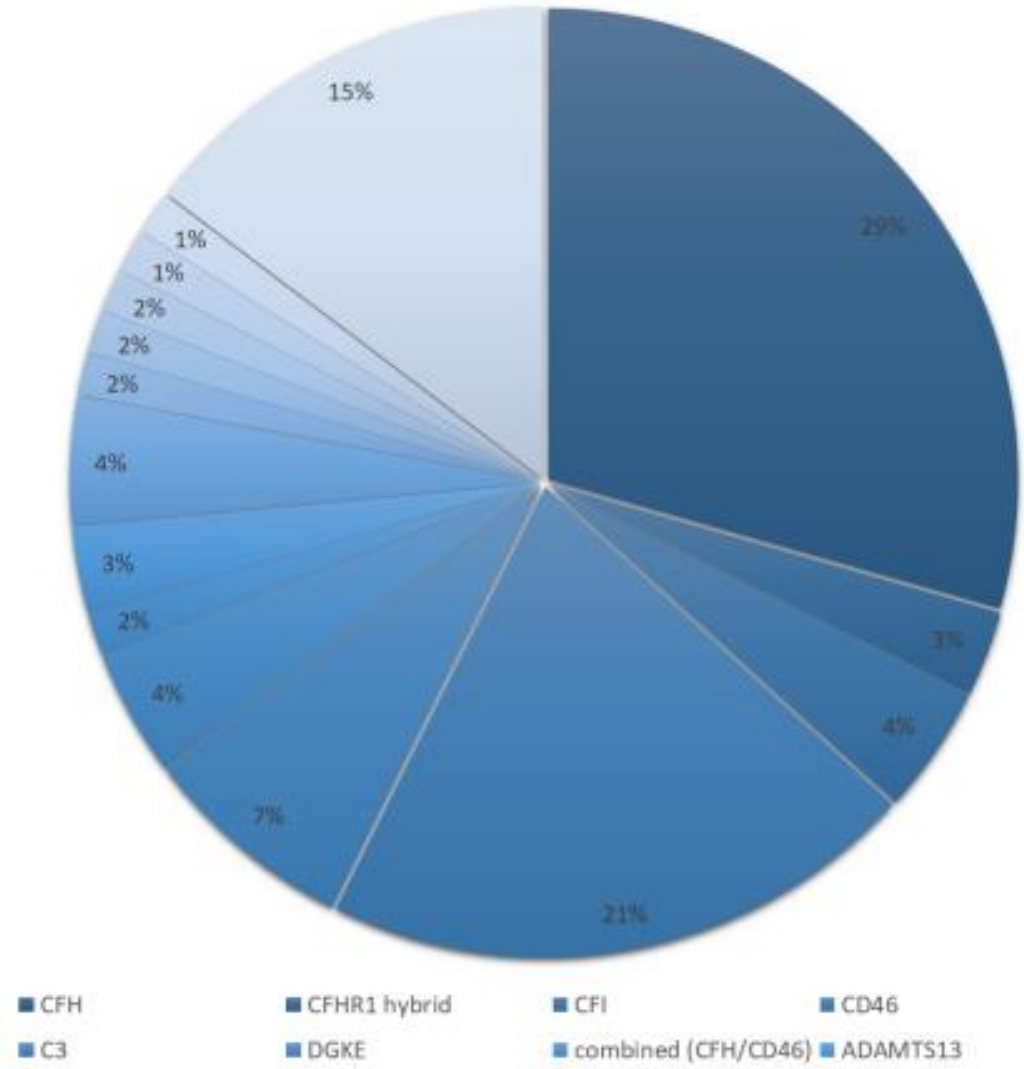



THRB
CFH
CFI
MCP
Regulation
CFB
C3
Activation
Loss-of-function mutations
Gain-of-function mutations
Complement system


Alternative pathway
Spontaneous activation, bacteria, bacterial toxins, LPS
C3
C3a
C3b
Ba
Factor B
Bb
C3 convertase
C3
C3a
C3b
C5 convertase
C5
C5a
C5b
C5b-9 (MAC)
anti-factor H
ΔCFHR1/3
Factor H
Factor I
MCP



Complement Mediated aHUS	
CFH including *CFH* hybrids	29.9%
CD46	20.9%
C3	7.5%
CFI	4.5%
CFHR1 hybrid	3%
Combined *CD46/CFH*	1.5%
Other	
DGKE	4.5%
ADAMTS13	3%
TSEN2	1.5%
INF2	4.5%
COL4A5	1.5%
CUBN	1.5%
GNE	1.5%
NRU4ATAC	1.5%
No gene identified	15%

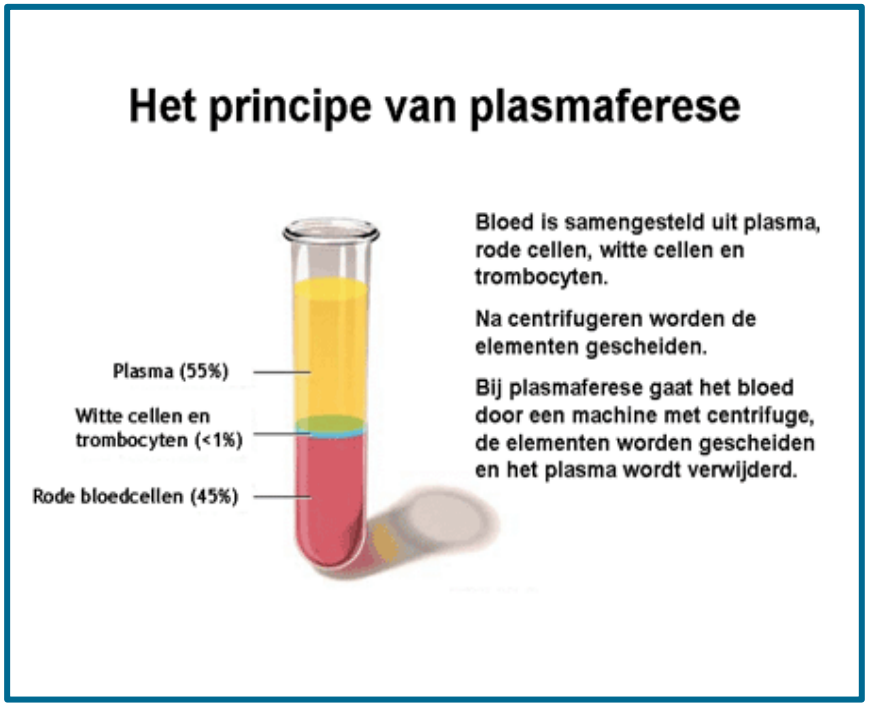
Symptomen bij aHUS

- Moe, algehele malaise, lusteloos, bleek zien, hoofdpijn, geel verkleuring oogwit
- Blauwe plekken
- Misselijk, minder-geen eetlust
- Minder plassen, veranderde kleur van de urine, hoge bloeddruk

Stellen van de diagnose aHUS / CaHUS

- Verhaal, symptomen in combinatie met bloed- en urine-onderzoek
- Uitsluiten van andere oorzaken
- Genetisch onderzoek , onderzoek antistoffen tegen complement

Behandeling aHUS vóór 2012



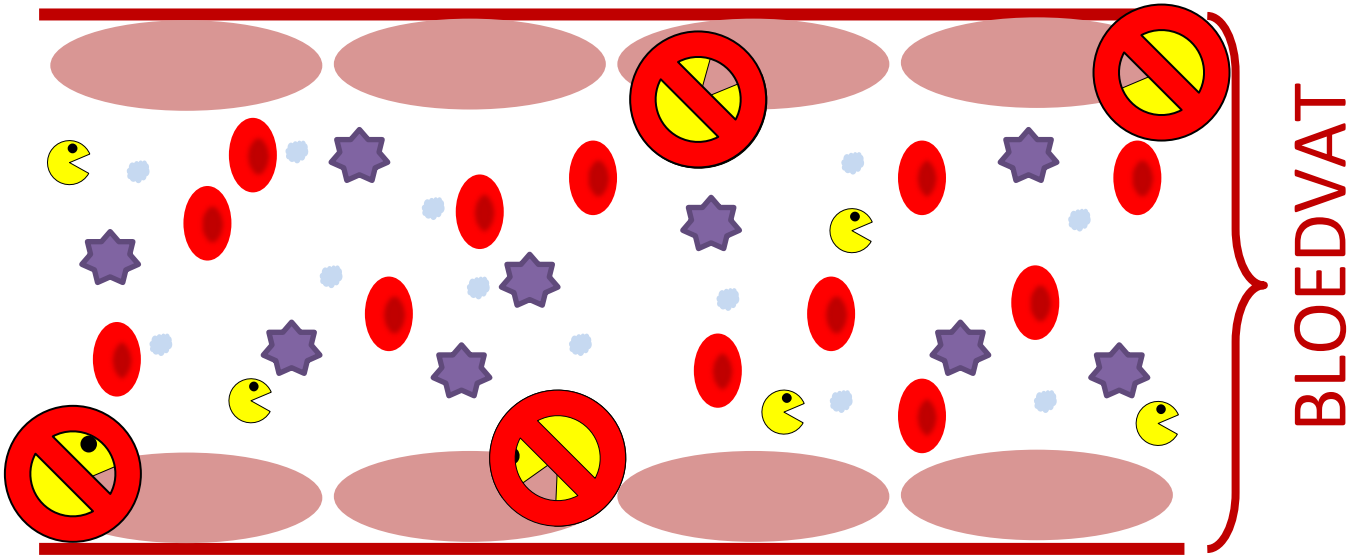
- aHUS eenmalig
- aHUS terugkomend een enkele keer
- aHUS recidiverend
- aHUS, plasma therapie afhankelijk

- Geen marker om te bepalen wie in welke groep zit
- Uitlokkende factoren: Infecties, medicatie, zwangerschap, hoge bloeddruk..

Behandeling aHUS na 2012

Eculizumab:
Blokkeert laatste stap complement (C5)

Complementsysteem en eculizumab

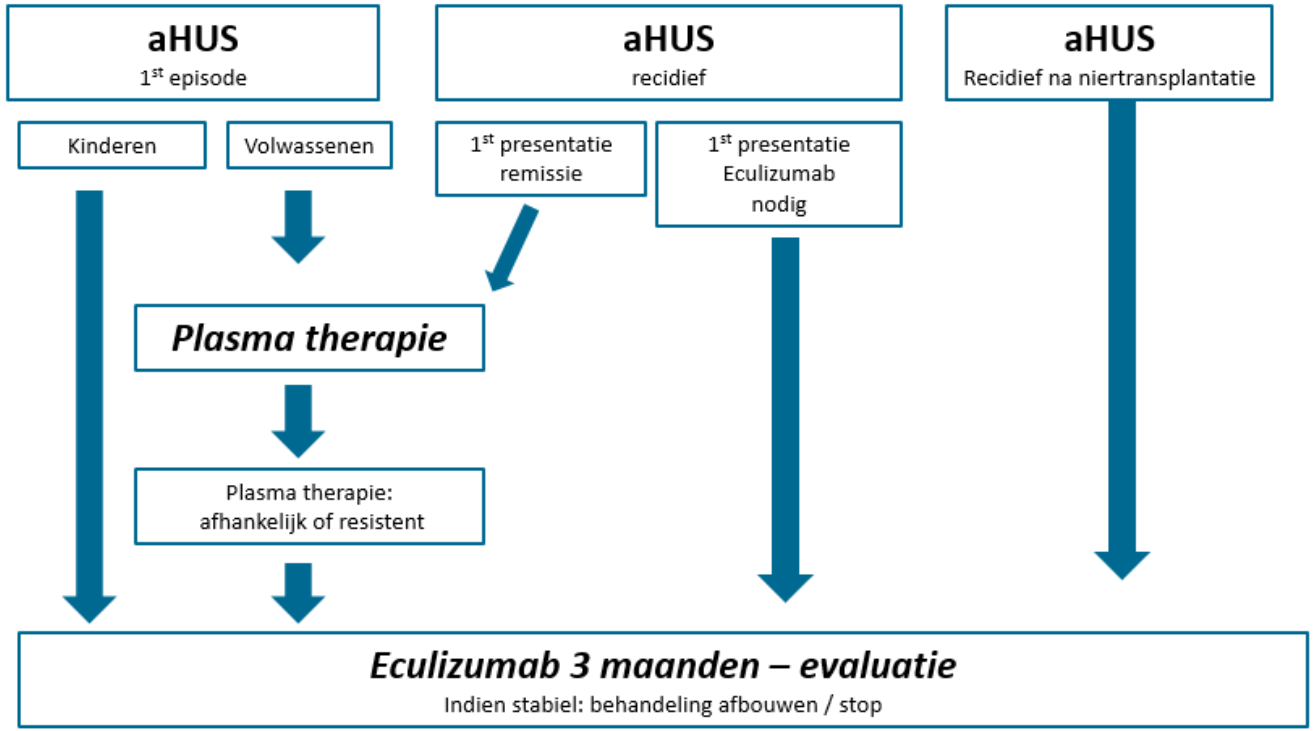


Landelijke werkgroep
Atypische HUS

Landelijke werkgroep: Nieuwe richtlijn diagnostiek en behandeling aHUS

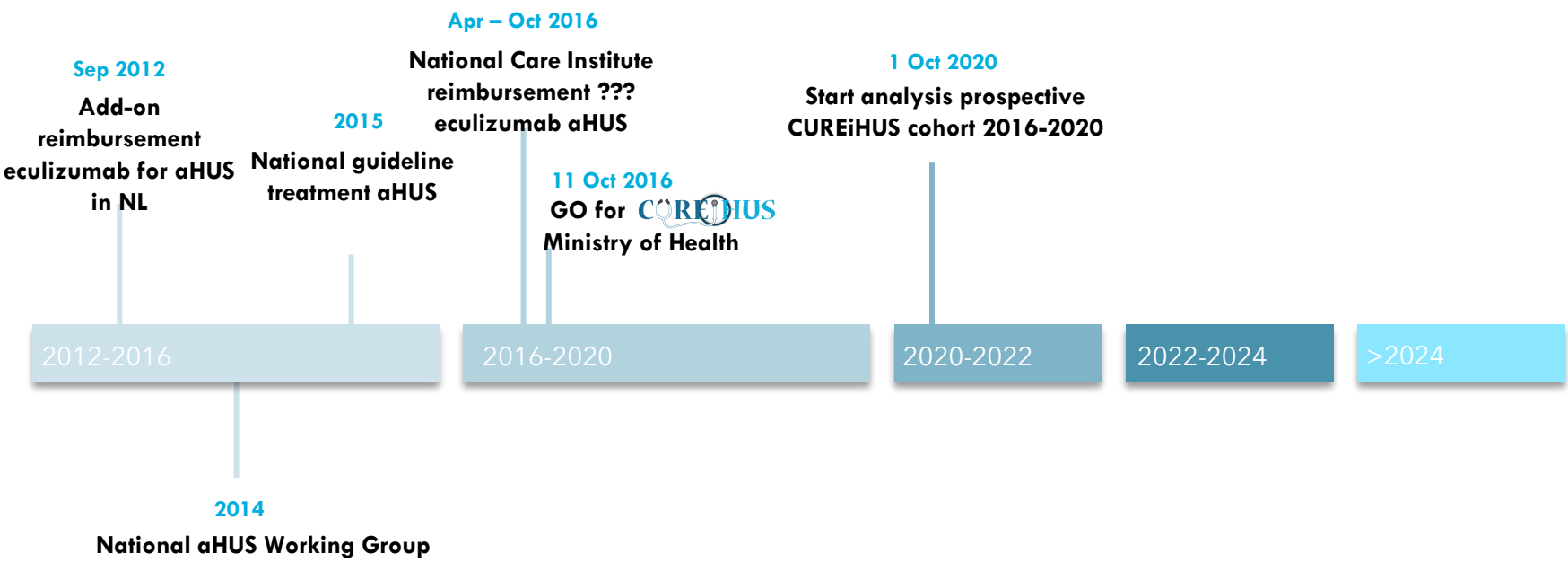
- Vanuit ieder academisch ziekenhuis in Nederland
  - Vertegenwoordiger nefroloog / kinderarts-nefroloog

Ziekenhuis	Nefroloog	Kinderarts-nefroloog
AUMC	Dr Bemelman	Dr Bouts / van Wijk
Erasmus	Dr Severs	Dr Dorresteijn
UMCG	Dr Eijgelsheim	Dr Gracchi
UMCU	Dr van Zuilen	Dr Keijzer-Veen
MUMC	Dr van Paassen	Dr Horuz
LUMC	Dr Bredewold	Dr van Rooij
Radboudumc	Dr van der Logt / Wetzels	Dr van de Kar


aHUS
1st episode
aHUS
recidief
aHUS
Recidief na niertransplantatie
Kinderen
Volwassenen
1st presentatie
remissie
1st presentatie
Eculizumab
nodig
Plasma therapie
Plasma therapie:
afhankelijk of resistent
Eculizumab 3 maanden – evaluatie
Indien stabiel: behandeling afbouwen / stop

Landelijke CUREiHUS studie > 2016

- Bij verdenking **aHUS**:
  - Contact met indicatie-commissielandelijke werkgroep aHUS
    - Eculizumab ja /nee
  - Geschiedenis en bloed-en aanvullende onderzoeken van patiënt
  - Starten met behandeling volgens landelijke richtlijn
    - Kinderen / volwassenen
    - Plasma / eculizumab
  - CUREiHUS studie evaluatie


Sep 2012
Add-on reimbursement eculizumab for aHUS in NL
2015
National guideline treatment aHUS
Apr – Oct 2016
National Care Institute reimbursement ??? eculizumab aHUS
11 Oct 2016
GO for CUREiHUS Ministry of Health
1 Oct 2020
Start analysis prospective CUREiHUS cohort 2016-2020
2014
National aHUS Working Group
2012-2016
2016-2020
2020-2022
2022-2024
>2024

In collaboration with **Dutch Kidney Patient Organization** and **National aHUS Working group**

CUREiHUS – 1e weesgeneesmiddelen-arrangement - Zorginstituut

- Nationale richtlijn met start- en stop criteria
- Indicatie-commissie
- Nationale Registratie – Data collectie – Kost-effectiviteit
- Evaluatie en monitoren

Eculizumab - aHUS

Stoppen Eculizumab

Vragen | Problemen

Antwoorden | Oplossingen

Praktische punten

Perspectief toekomst

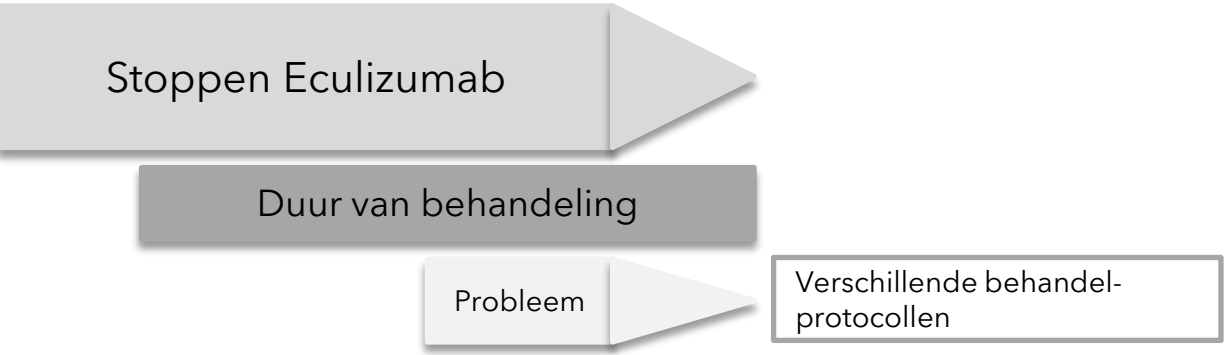
Het stoppen van eculizumab

Stoppen Eculizumab

- Duur van behandeling
- Uitkomsten stoppen

Author (et al) Year of publication	**Cohort | discont*** *Children | Ntx	**Eculizumab treatment** Range	**Follow-up duration** Range	**Relapse Rate** n=	**Time to Relapse** Range	**Outcome Relapse**
Prospective studies						
Bouwmeester 2022	**21 | 21** 7 | 0	**3.3 mo** 0.5-7.2	**20.2 mo** 0.0-60.0	**22%** 4/18	**3.6 mo** 1.8-15.5	No chronic sequelae in relapsing patients
Fakhouri 2021	**55 | 55** 19 | 3	**16.5 mo** 1.0-59.0	**19.8 mo** 5.4-24.0	**22%** 12/54	**10.2 mo** 1.6-22.1	Eculizumab resumed with no significant change in GFR
Chaturvedi 2021	**31 | 25** 0 | 0	**2.4 mo** 1.1-9.67 IQR	**27.0 mo** 5-50 IQR	**20%** 5/25	-	No change in eGFR in 4/5. One patient died during recurrent TMA (nonadherent with therapy)
Menne 2019	**93 | 42** 17 | 9	**19.6 mo** 0.2-86.9	NA	**26%** 11/42	**<30 mo** -	40% decline in kidney function after discontinuing: but eGFR remained .60 mL/min/1.73 m2
Retrospective studies	Total/Mean					
Ardissino (14), Sheerin (16), Fakhouri (16), Wijnsma (2017), Merrill (2017), Ariceta (2017)	**247** -	**7.7 mo** 3.0-17.5	**16.5 mo** 7.9-27.4	**28%** 14-44	**3.7 mo** 1.2-7.5	*Overall: if adequately retreated no chronic sequelae*

Het stoppen van eculizumab



Author (et al) Year of publication	**Cohort | discont*** *Children | Ntx	**Eculizumab treatment** Range	**Follow-up duration** Range	**Relapse Rate** n=	**Time to Relapse** Range	**Outcome Relapse**
Prospective studies						
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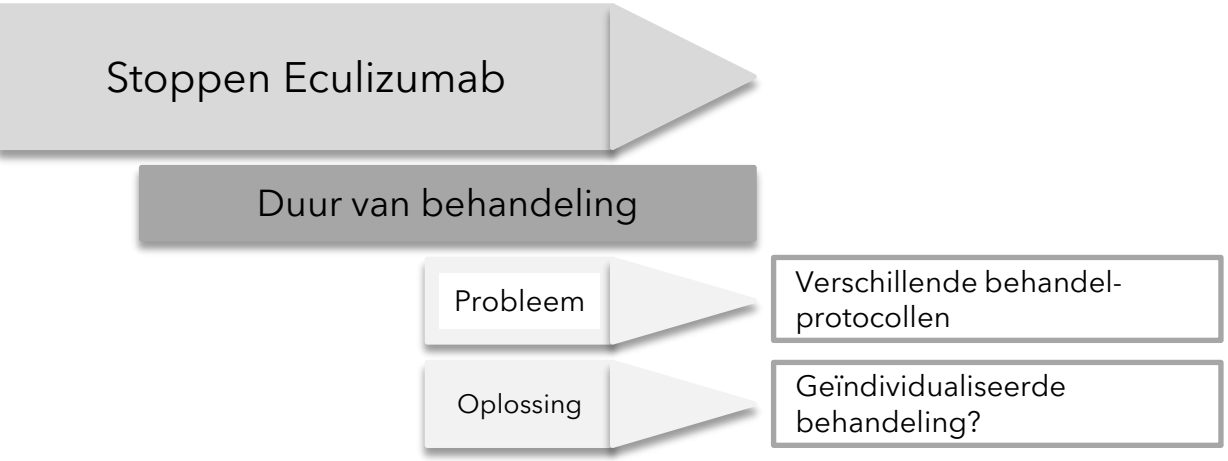

Stoppen Eculizumab
Duur van behandeling
Probleem
Verschillende behandel-protocollen
Oplossing
Geïndividualiseerde behandeling?

Eculizumab dosering schema – Inductie

5 - 10 kg

Week 1 and 2: 300 mg/dosis 1 x week
Then: 300 mg/dosis 1 x 3 weeks

10 - 20 kg

Week 1: 600 mg/dosis 1 x week
Week 2: 300 mg/dosis 1 x week
Then: 300 mg/dosis 1 x 2 weeks

20 - 30 kg

Week 1 and 2 and 3: 600 mg/dosis 1 x week
Then: 600 mg/dosis 1 x 2 weeks

30 tot 40 kg

Week 1 and 2: 600 mg/dosis 1 x week
Week 3: 900 mg/dosis 1 x week
After: 900 mg/dosis 1 x 2 weeks

≥ 40 kg

Week 1,2,3,4: 900 mg/dosis 1 x week
Week 5: 1200 mg/dosis 1 x week,
After: 1200 mg/dosis 1 x 2 weeks

Table 5.

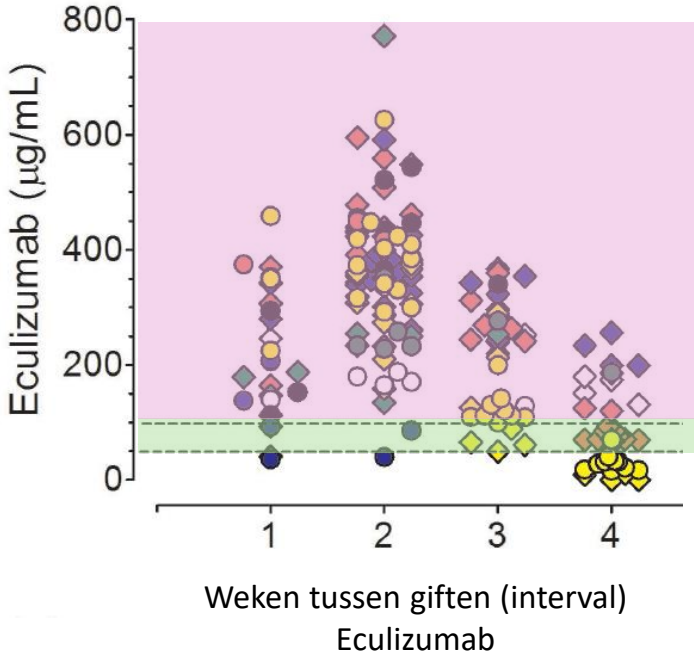
Alternative loading dose strategy for eculizumab

	Induction phase	Maintenance phase	
Patient weight (kg)	**Day 1**	**Day 15**	**Beyond**
≥120	2400 mg	1200 mg	Standard maintenance dosing (Table 1)
90–120	2100 mg	1200 mg	
60–90	1800 mg	1200 mg	
40–60	1500 mg	1200 mg	
30–40	900 mg	900 mg	
20–30	600 mg	600 mg	
10–20	600 mg	300 mg	
5–10	300 mg	300 mg	

Standaard oplaad dosering:
5% niet compleet geblokkeerd complement in 1e week van behandeling

Alternatief schema:
Iedereen compleet geblokt in 1e week van behandeling

Ter Avest M, Bouwmeester RN, Duineveld C, et al. Proposal for individualized dosing of eculizumab in atypical haemolytic uraemic syndrome: patient friendly and cost-effective. NDT. 2022



CH50 <30%

Volokhina E et al, Clinical Pharmacology & Therapeutics 2017

Ardissino et al. Complement functional tests for monitoring eculizumab treatment in patients with atypical hemolytic uremic syndrome: an update. Pediatr Nephrol. 2018

Radboudumc

Stoppen eculizumab

- Duur van behandeling
- Uitkomsten stoppen
  - Recidief ?
  - Risico recidief
  - Kosten-effectiviteit
  - Patient ervaringen

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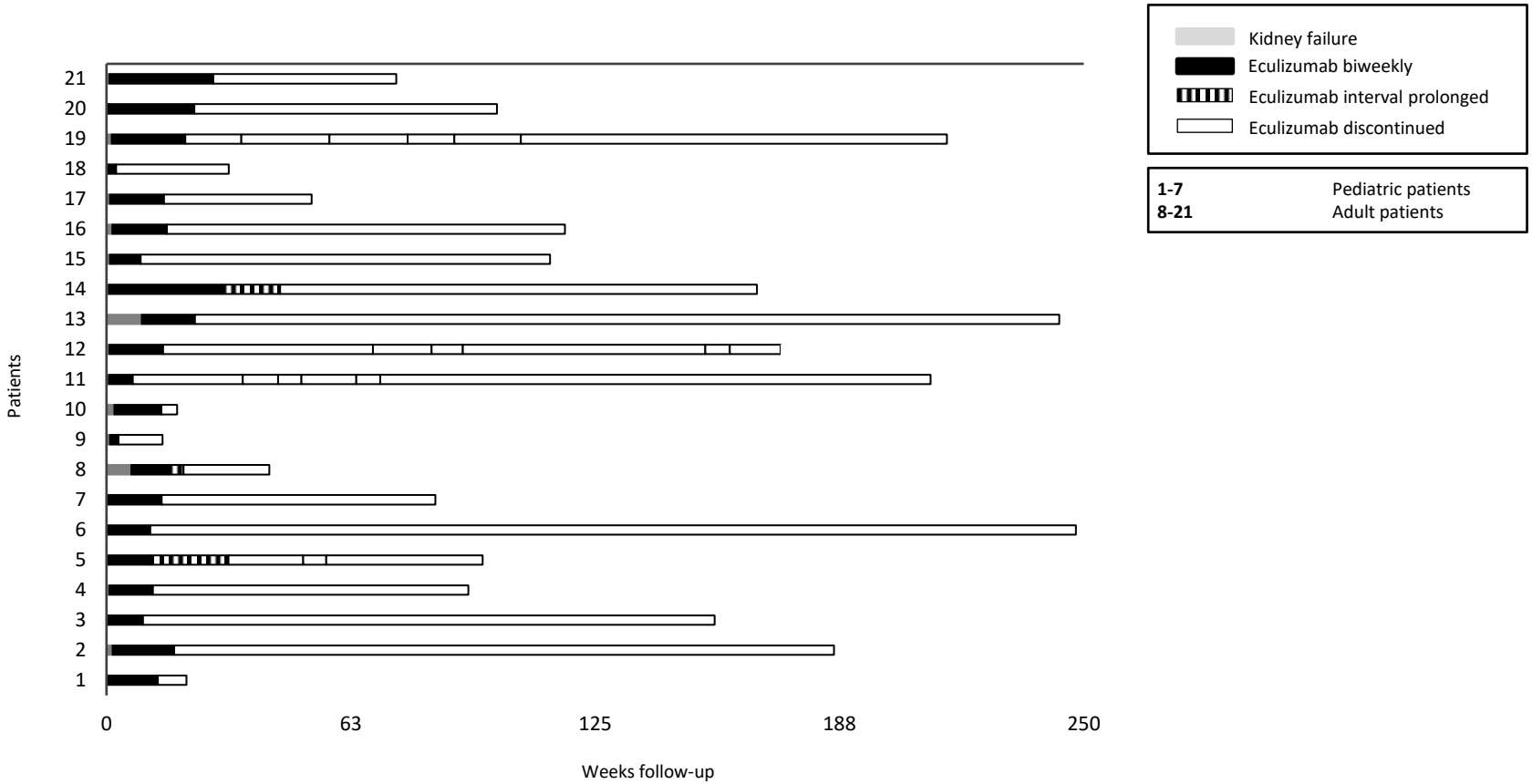
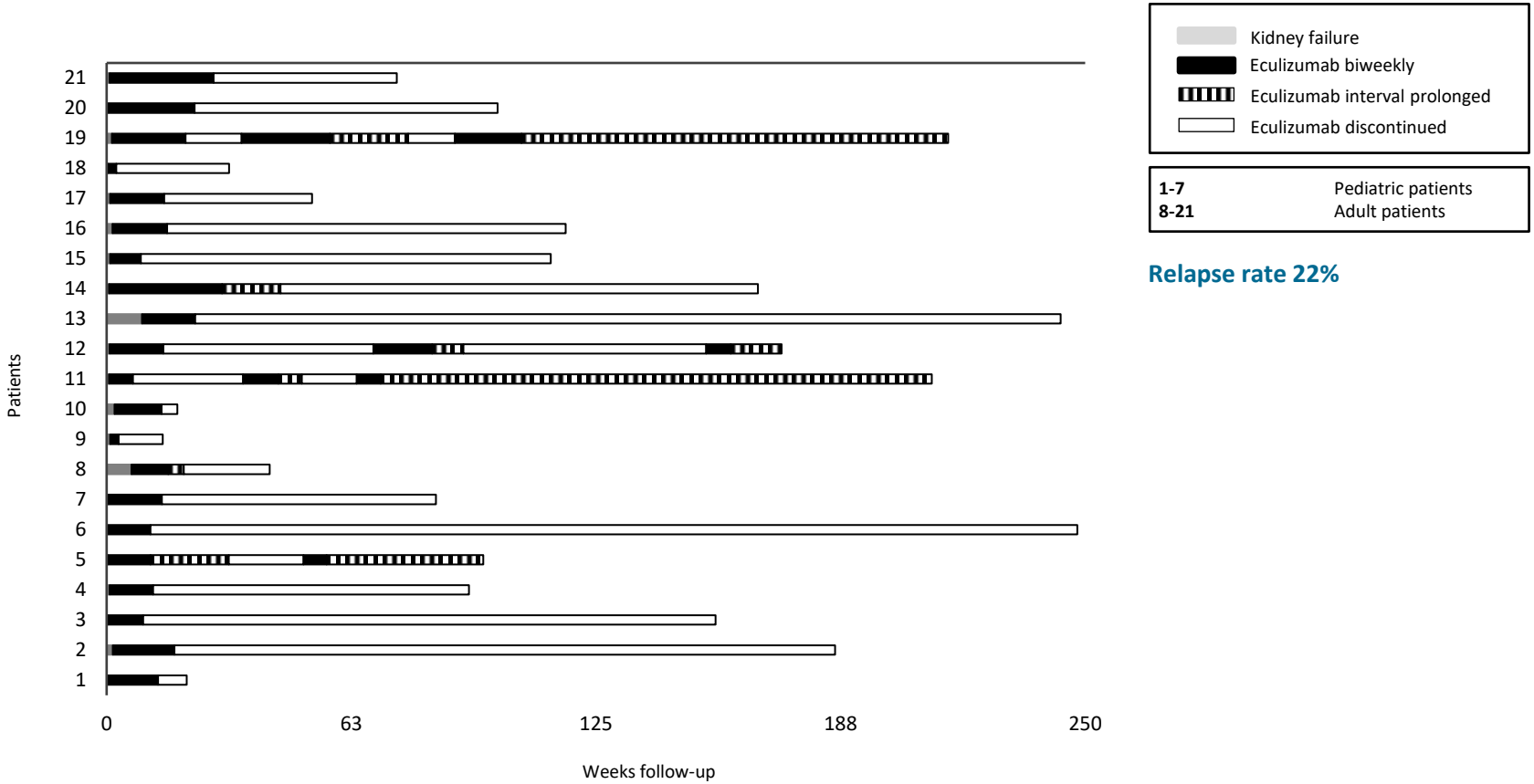


Median follow-up duration: 99.9 weeks (14.3-248.0)
Median follow-up duration after discontinuation: 80.7 weeks (0.0-236.9)



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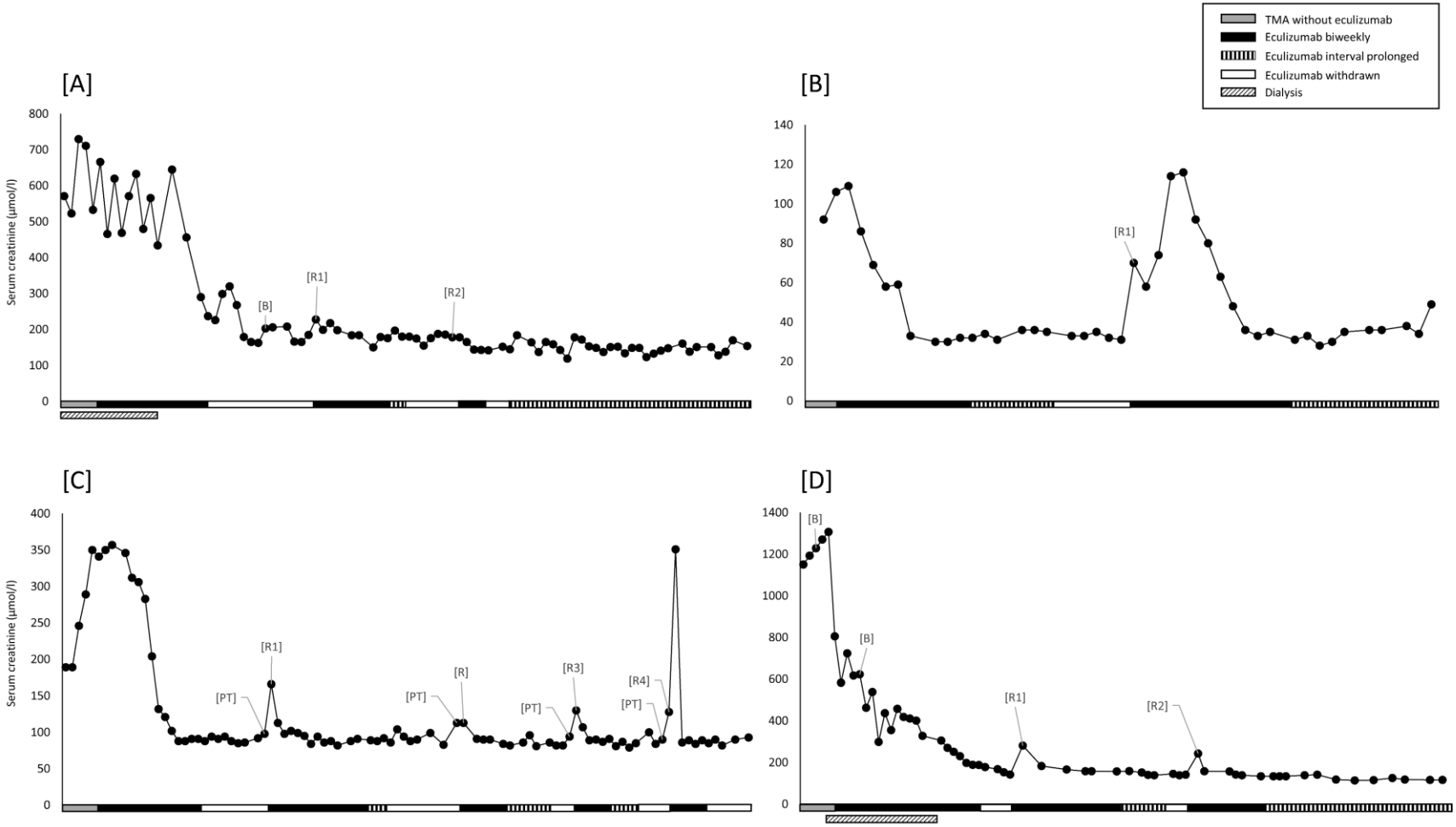

Serum creatinine concentrations over time in the 4 relapsing patients

Bouwmeester et al. Kidney Int Reports 2022

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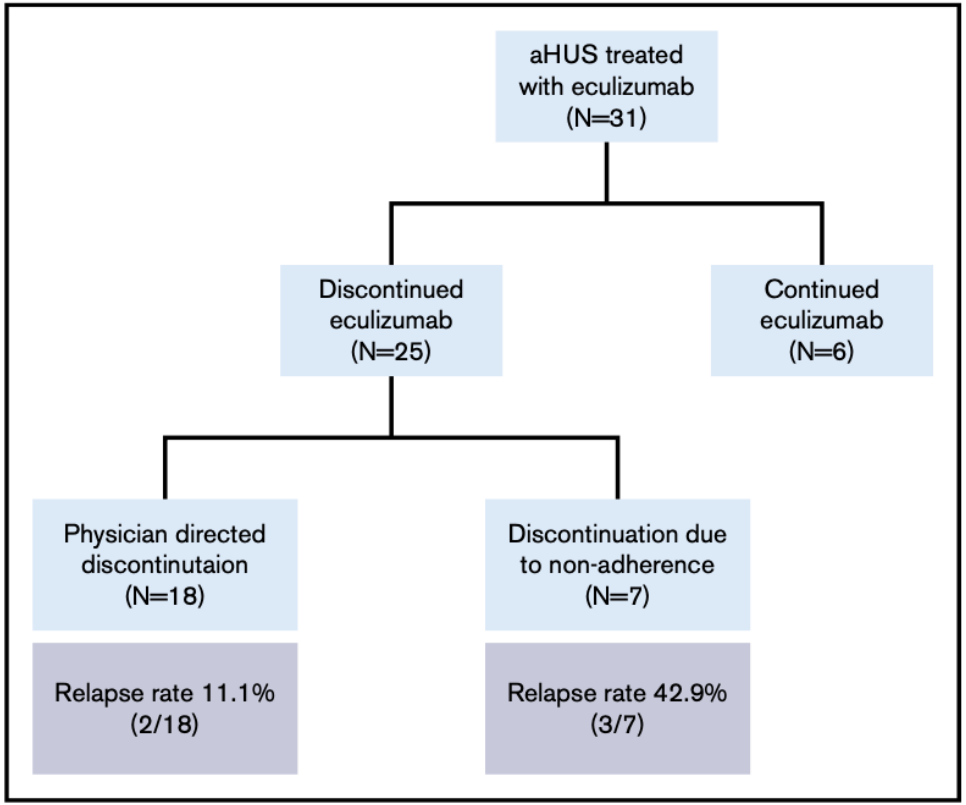
Op tijd herstarten eculizumab?



Chaturvedi S et al. Outcomes of a clinician-directed protocol for discontinuation of complement inhibition therapy in atypical hemolytic uremic syndrome. Blood Advances 2021

Stoppen eculizumab

- Duur van behandeling
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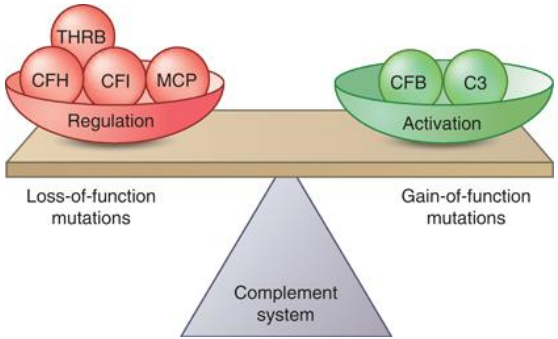


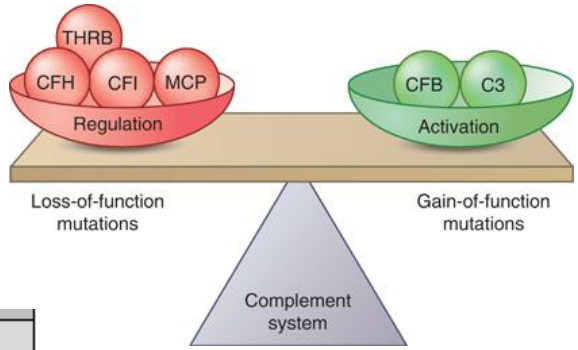
Table 1 Complement-related genetic mutations in aHUS. Various clinical outcomes and the relationship with the different complement-related genetic mutations involved in aHUS

		Function in complement system	Frequency in aHUS (%)	ESRD after 5 years (%)	Recurrence (%)	Recurrence after kidney transplantation (%)	References
FH	Factor H	Co-factor for factor I	21–25	70–80	30–50	68–90	[5, 8, 10–14, 19, 25, 28–31]
MCP/CD46	Membrane co-factor protein	Membrane-bound complement regulator	5–22.8	10–50	58–90	11–20	[5, 8, 10–13, 29–31]
FI	Factor I	Inactivation of C3b and C4b	6–16.6	45–60	10–30	70–80	[5, 8, 10, 12, 13, 29–31]
FB	Factor B	Allows the formation of C3 and C5 convertases	1.9–4	70	Rare	Rare	[5, 8, 10, 13]
C3	Complement C3	Necessary for complement cascade activation	6–9	45–65	50	40–50	[5, 8, 10, 12, 13]
FHRs	Factor H-related proteins	Circulating proteins similar to factor H associated with autoantibodies against FH	4.5–35	30–63	23–60	20	[8, 10, 12, 13, 30]
FHR hybrid genes	Factor H, Factor H-related proteins	See function FH and FHRs	1–5	–	–	–	[8, 10]
THBD/CD141	Thrombomodulin	Degradation C3b	2–5	53–60	23–30	Rare	[5, 8, 10, 13]

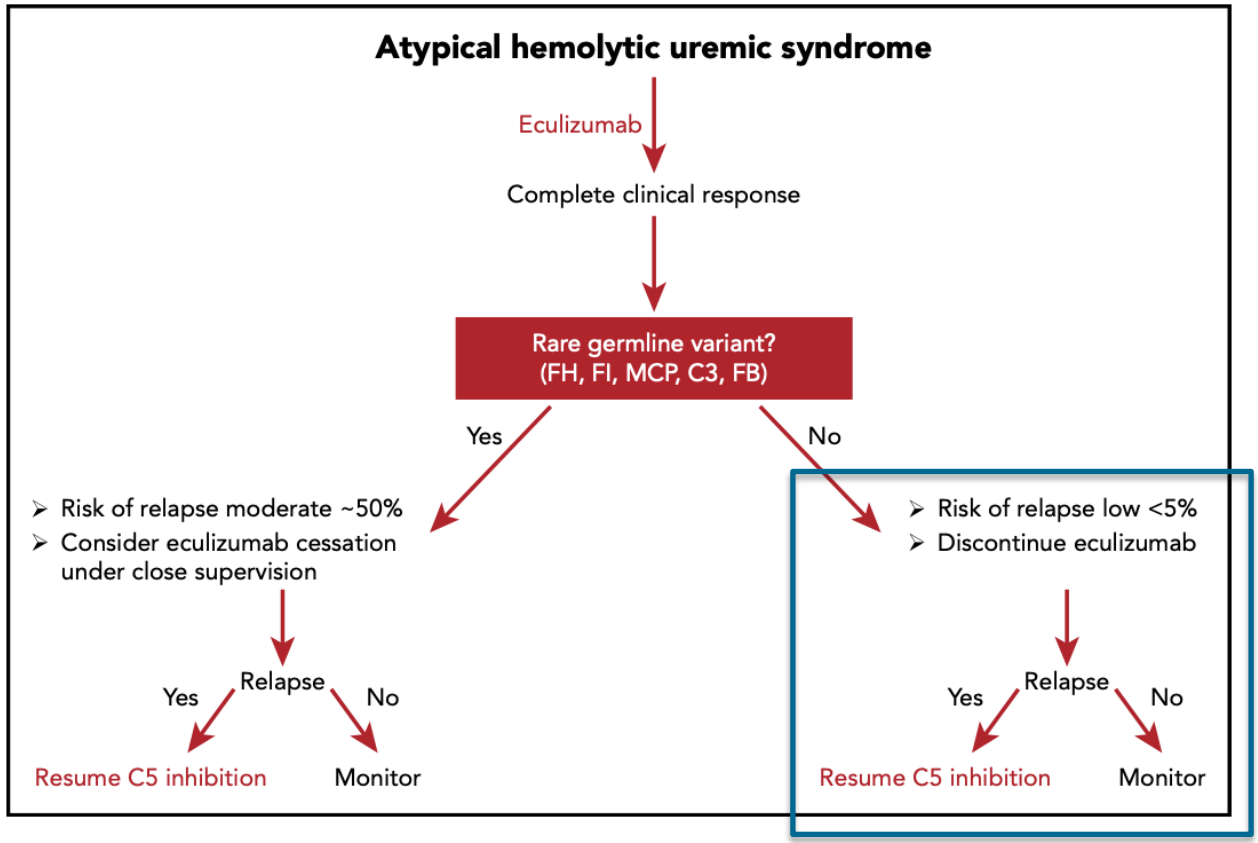
FH factor H, **MCP/CD46** membrane cofactor protein, **FI** factor I, **FB** factor B, **FHR** factor H-related proteins, **THBD/CD141** thrombomodulin, **aHUS** atypical hemolytic uremic syndrome, **ESRD** end-stage renal disease

Feitz et al. Medizinische Genetik 2018

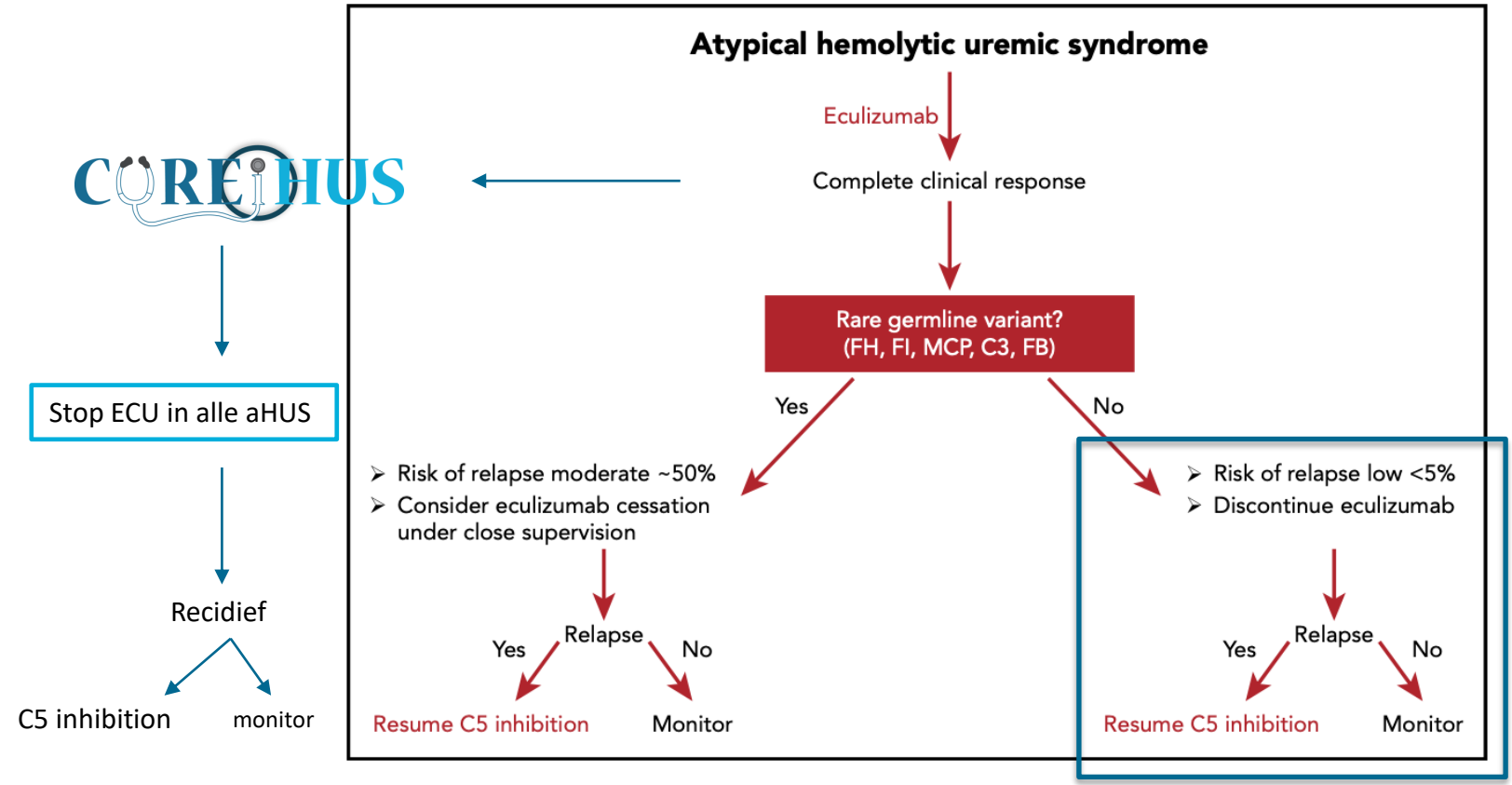
CORE HUS



	No relapse (n=14)	Relapse(s) (n=4)
Sex		
Female	8 (57.1%)	1 (25%)
Male	6 (42.9%)	3 (75%)
Median age (years)	28.6 (3.1-78.5)	29.5 (3.7-37.8)
Children	5 (35.7%)	1 (25%)
Adults	9 (64.3%)	3 (75%)
Patients with a complement genetic variant[1]	10 (71.4%)	4 (100%)
CFH[2]	6 (42.8%)[11]	1 (25%)
MCP	3 (21.4%)	0 (0%)
CFI	1 (7.1%)	1 (25%)
C3	3 (21.4%)	3 (75%)
CFB	0 (0%)	0 (0%)
Patients with >1 complement genetic variants[1]	2 (14.3%)	1 (25%)
Anti-factor H antibodies	2 (14.3%)	0 (0%)
Patients with a complement genetic variant[1] and:		
MCP*ggaac* haplotype homozygosity	2 (14.3%)	1 (25%)
CFH-H3 haplotype homozygosity	1 (7.1%)	0 (0%)

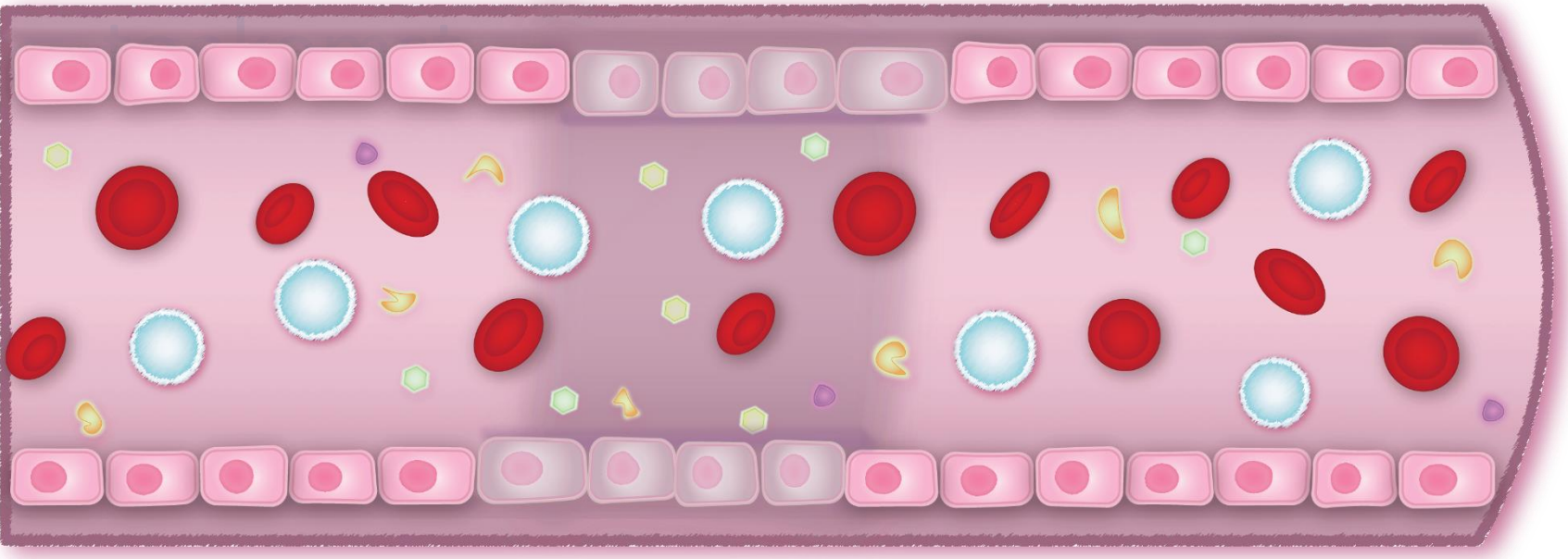


Brodsky RA. Blood 2021.



Brodsky RA. Blood 2021.

Tijdige herkenning?



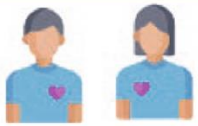
Haemoglobinuria for the early identification of aHUS relapse. Data from the ItalKId-HUS Network.

Journal of NEPHROLOGY
Springer Link

aHUS is a thrombotic microangiopathy involving the glomerulus and associated with renal damage. Thus it cannot take place without haematuria.

aHUS patients could be monitored for relapses with urine dipstick or urinalysis for haemoglobinuria.

Retrospective study to analyse our experience on aHUS patients
- who have never be treated with C5 inhibition;
-who are on treatment;
- who have discontinued treatment.



84 patients

1517 determinations

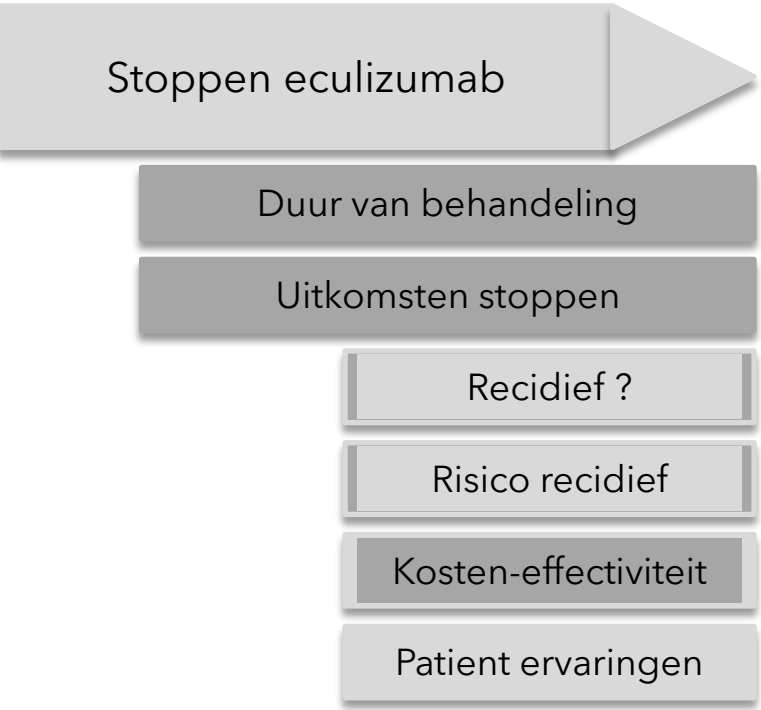
8904 patient-month

	Relapse n. (%)	No relapse n. (%)	Total
uHb+	21 (10.0)	188 (90.0)	209
uHb-	0 (0)	1308 (100)	1308
Total	21 (1.4)	1496 (98.6)	1517

Sensitivity 100% and Specificity 87.4%
PPV 10.5% and NPV 100 %.
Accuracy 87.6%.

Conclusion: Haemoglobinuria is a very sensitive and acceptably specific marker of aHUS relapse. This finding and its validation may have a positive impact on patients' quality of life and on the outcome of this life threatening disease via an early diagnosis of relapses.

M. Brambilla, GL. Ardissino, F. Paglialonga, S. Testa, V. Capone, G. Montini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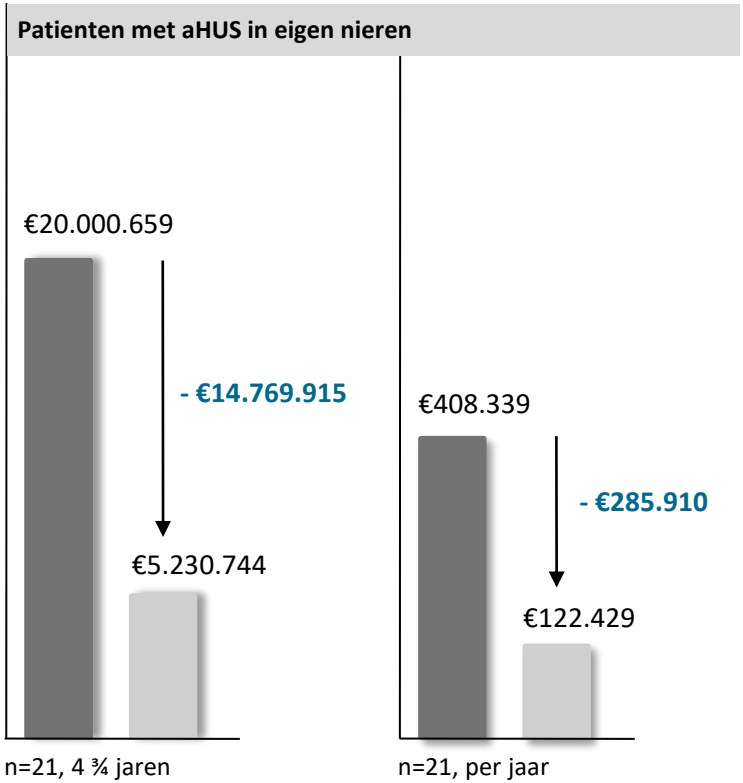

Bouwmeester et al. Kidney Int Rep 2022.

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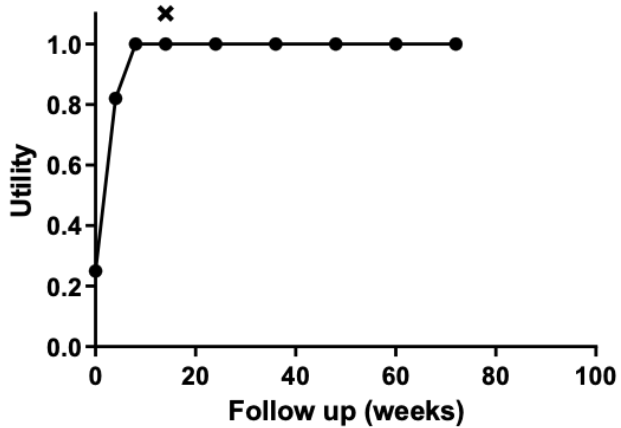


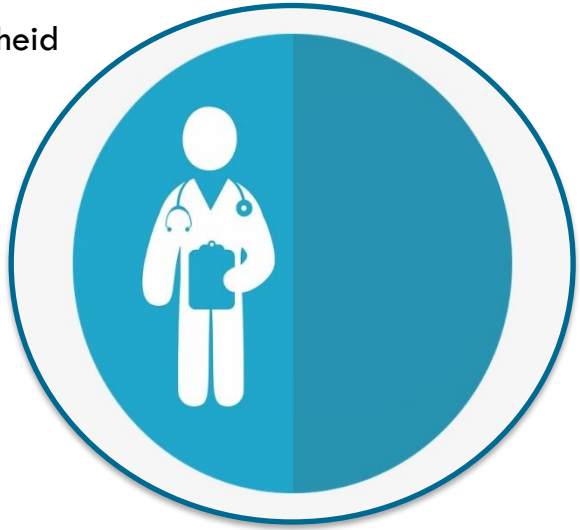
Praktische punten

Duur van de behandeling

- **Geindividualiseerde behandeling,** inductie en onderhoud doseringen: optimalisatie 1e dosering en interval verlenging (3-4 wk)
- **Eerder stoppen** indien volledige herstel nierfunctie**,** maar ook indien geen herstel nierfunctie

Tijdige herstart eculizumab!!!

- Beschikbaarheid - bereikbaarheid
- Goede instructies
- Adequate monitoring:
  hematuria/proteinuria
- Thuis metingen:
  bloeddruk/ urinestick



- Patient betrokkenheid
- Pro-actief

Toekomst perspectieven

Grotere data registratie:

- Unbiased stoppen
- Langere follow-up: lange-termijn risico's?

Biomarkers vroege detectie van ziekteactiviteit

Versnelde DNA diagnostiek (2wk)

Andere nieuwe complement inhibitors

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Drug	Target	Mechanism	Clinical trial number
Atypical hemolytic uremic syndrome			
Iptacopan oral	Factor B	Prevents formation of C3 and C5 convertases	**NCT04889430 Phase III, adults**
Pegcetacoplan (s.c.)	C3	Prevents formation of C3 and C5 convertases	NCT05148299 Phase II postBMT-TMA
Crovalimab (i.v. then monthly s.c.)	C5	Prevents formation of C5 convertase	**NCT04858265** **NCT04861259**
Avacopan oral	C5aR1	Blocks anaphylatoxin formation (C3a, C4a and/or C5a)	NCT02464891 Phase II, pts on dialysis
Narsoplimab (i.v. then daily s.c.)	MASP2	Blocks initiation of lectin pathway	**NCT03205995**

Dank voor uw aandacht!

nicole.vandekar@radboudumc.nl www.atypischehus.nl