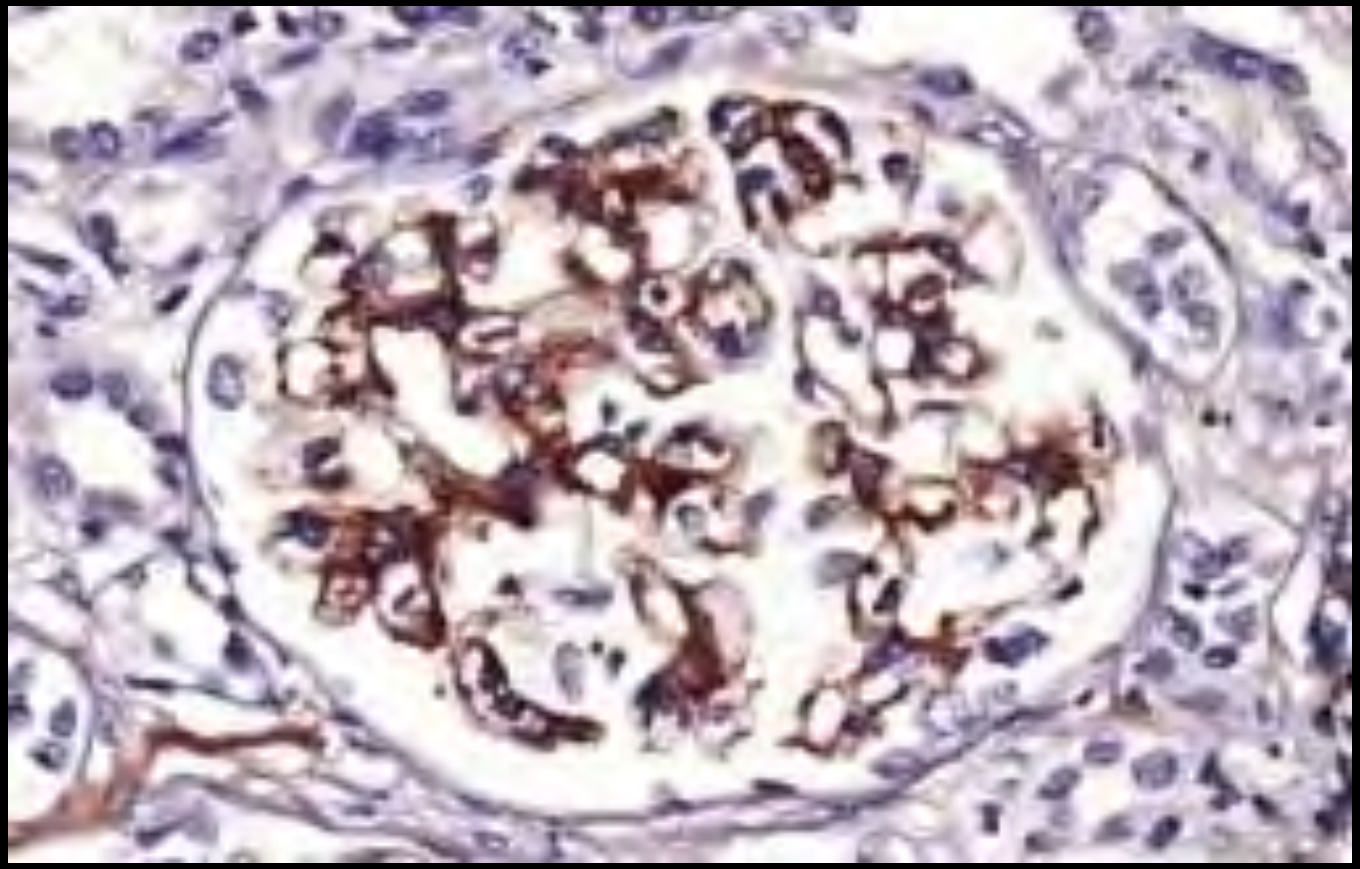
# Themadag specifieke diagnoses: Dense Deposit Disease



Cees van Kooten & Darius Soonawala
Afd Nierziekten LUMC

30 sept 2017

# Het programma voor vanochtend

- Uitleg over achtergrond ziekte
  - De naamgeving
  - Functioneren van de nier
  - Afweer en Complement – C3
- Diagnostiek
- Behandeling en prognose
- Nieuwe ontwikkelingen
  - Medicijnen
  - Onderzoek
- Vragen

# Dense Deposit Disease (DDD)

Membrano Proliferative Glomerulonephritis type II (MPGN-II)

C3 Glomerulonephritis (C3-GN)

C3G – C3 glomerulopathie

? ? ? ? ?

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# Dense Deposit Disease (DDD)

Membrano Proliferative Glomerulonephritis type II (MPGN-II)

C3 Glomerulonephritis (C3-GN)

C3G – C3 glomerulopathie

*-glomerulus = filter van de nier*
*-nephritis = nierontsteking*
*-pathie = ziekte*

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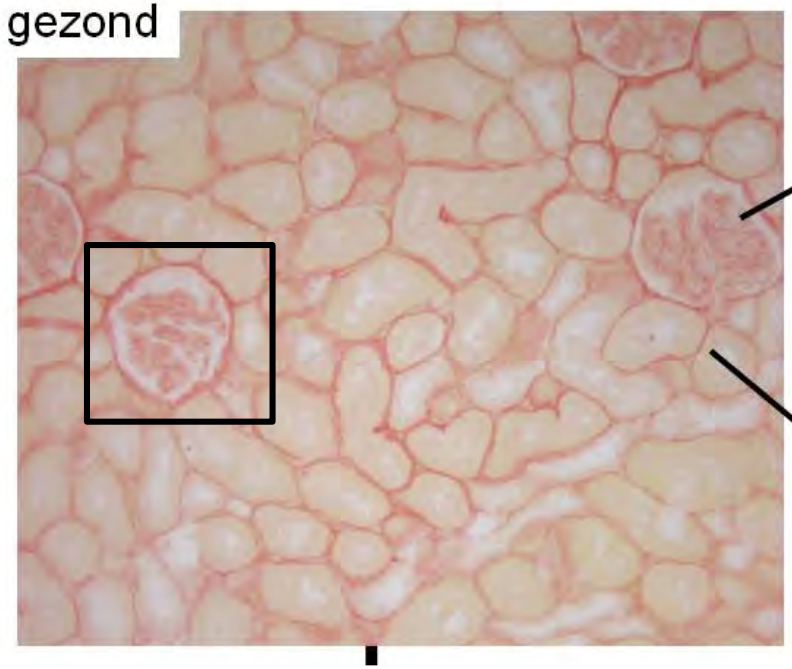
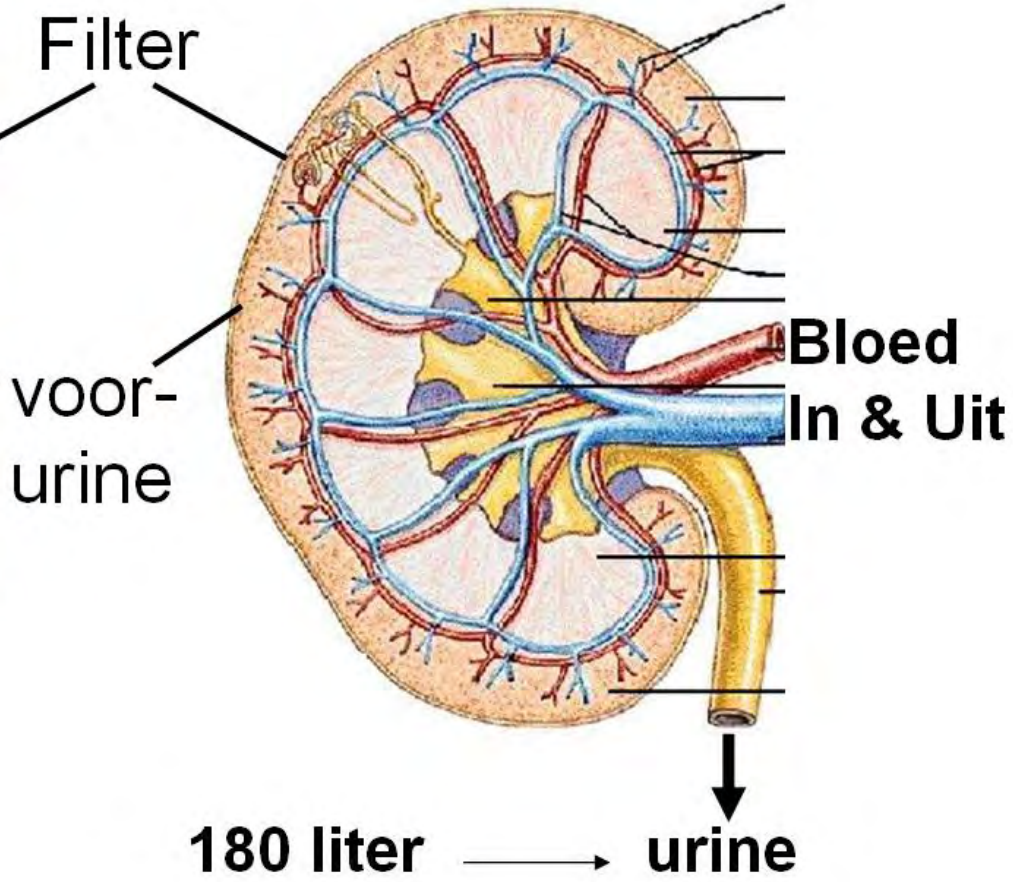
# De functie van de nier




**Bloedzuivering**

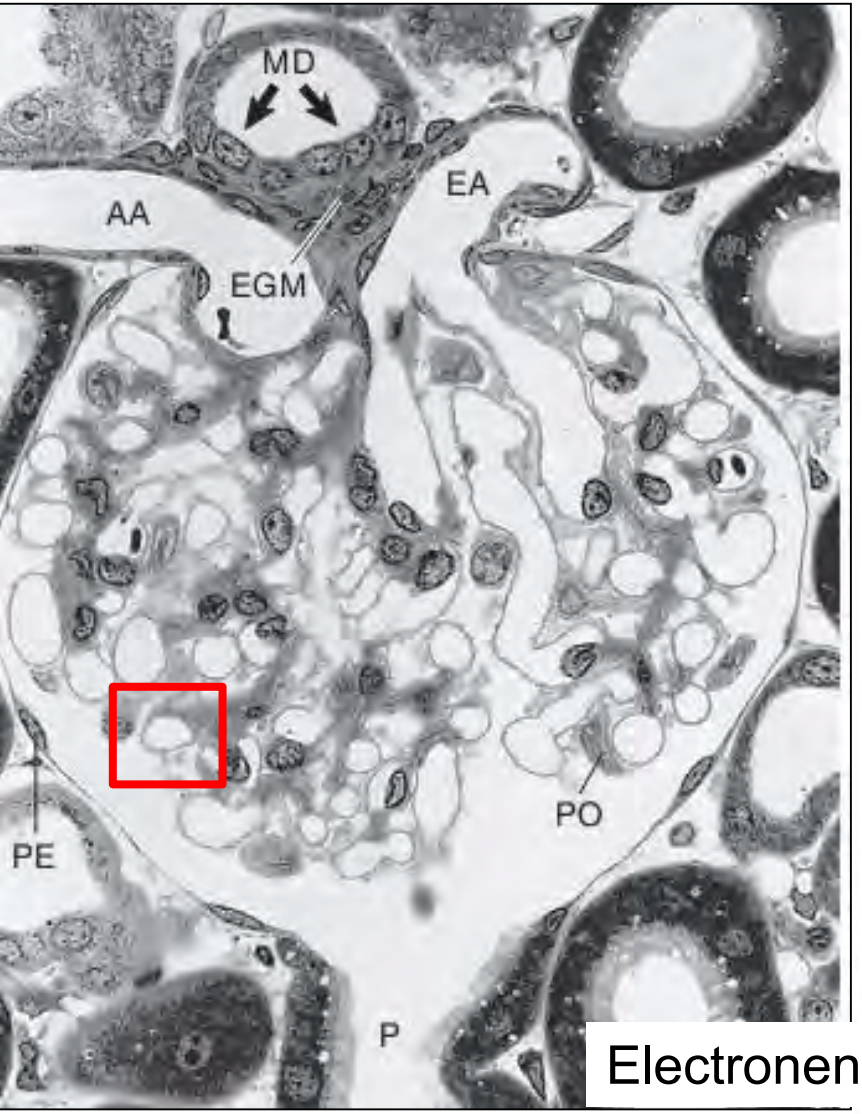
**Regelt Bloeddruk**

**Produceert hormonen (bv EPO)**

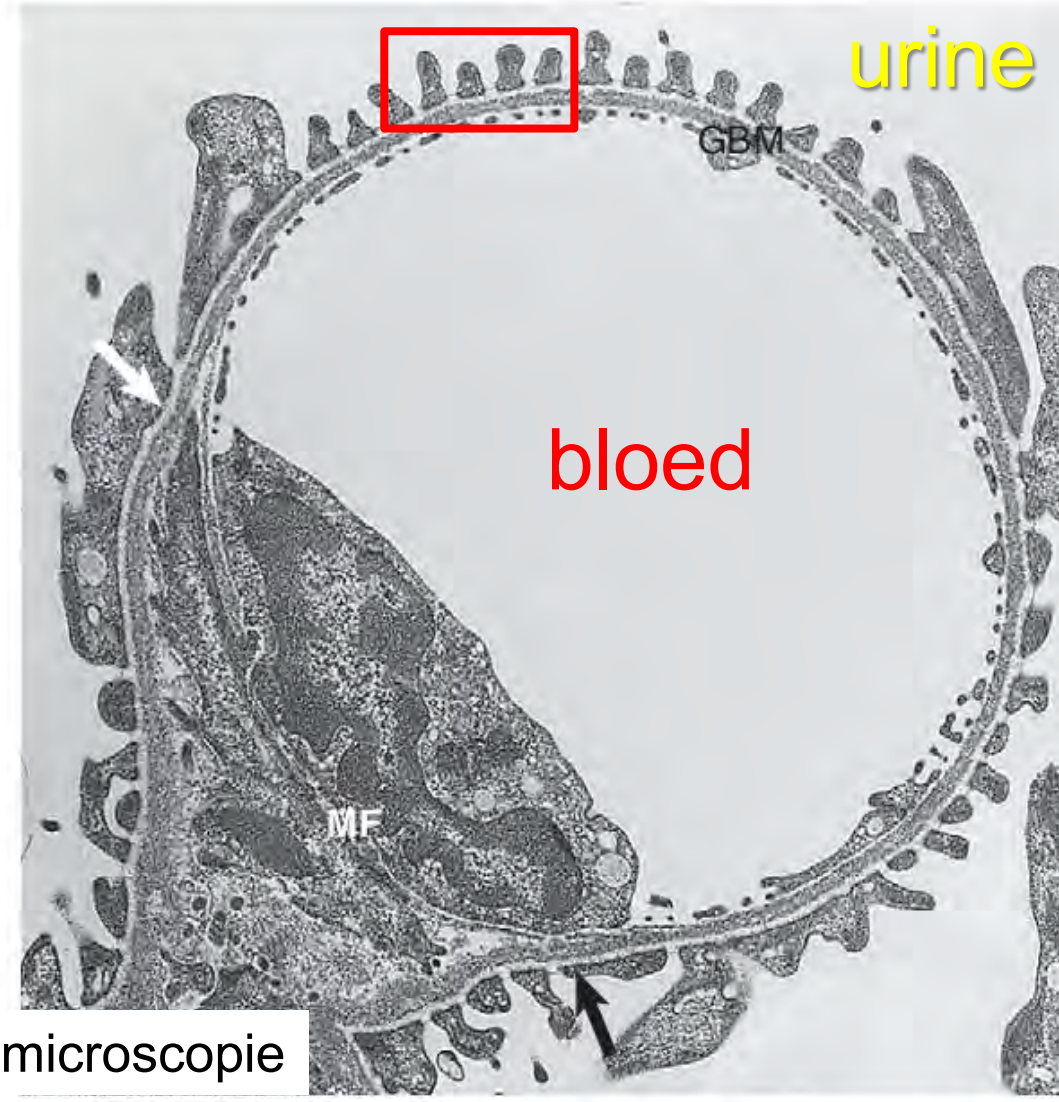
**Regelt vochtverdeling in lichaam**

# Inzoomend op de nier

Glomerulus = Filterlichaampje

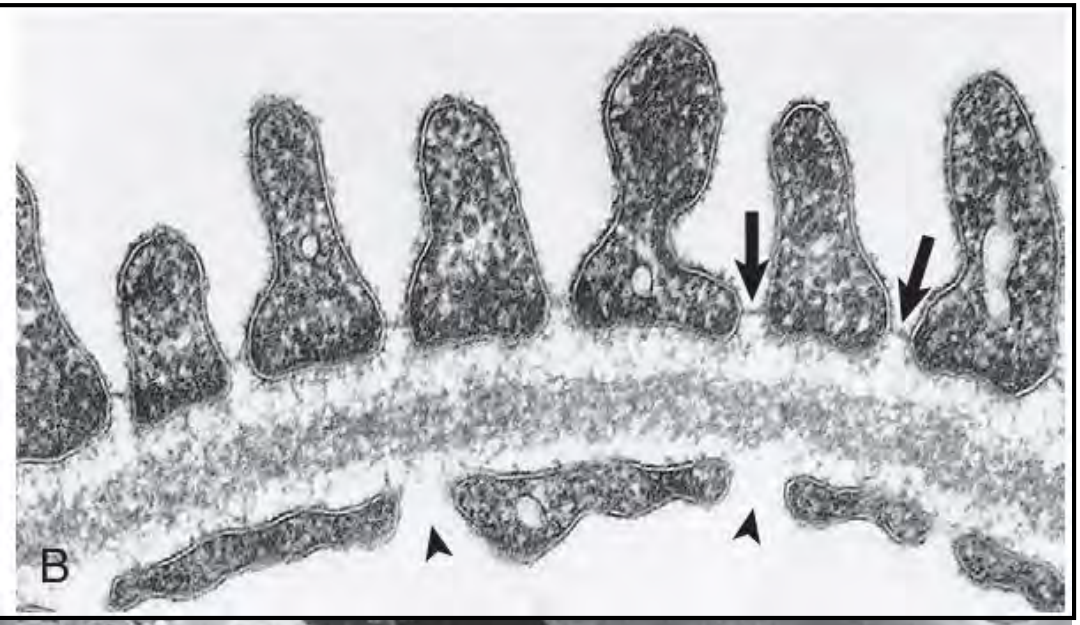


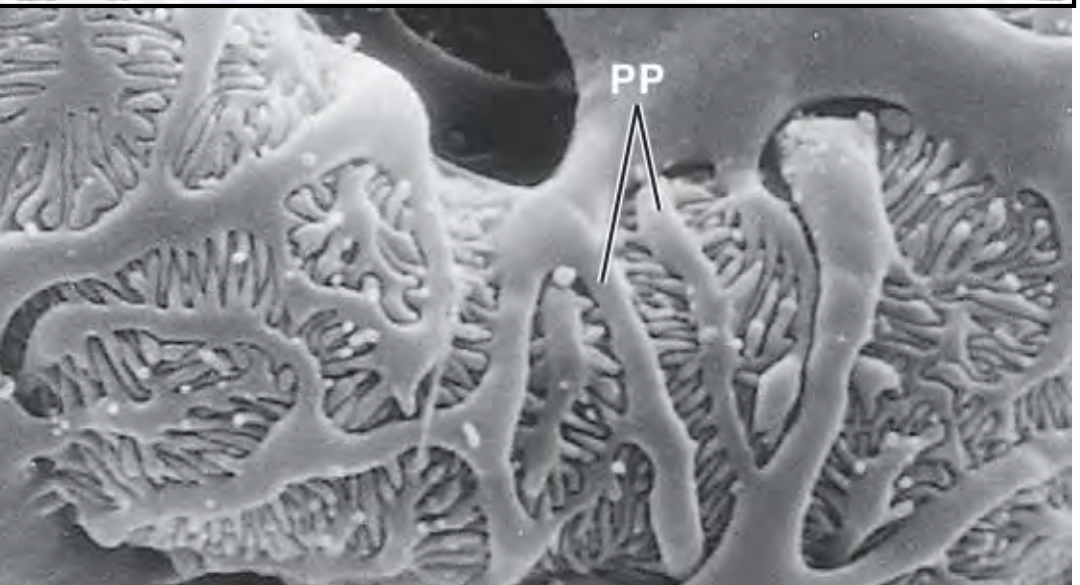

Capilair Bloedvaatje




Electronenmicroscopie

# Inzoomend op de nier




Het Filter

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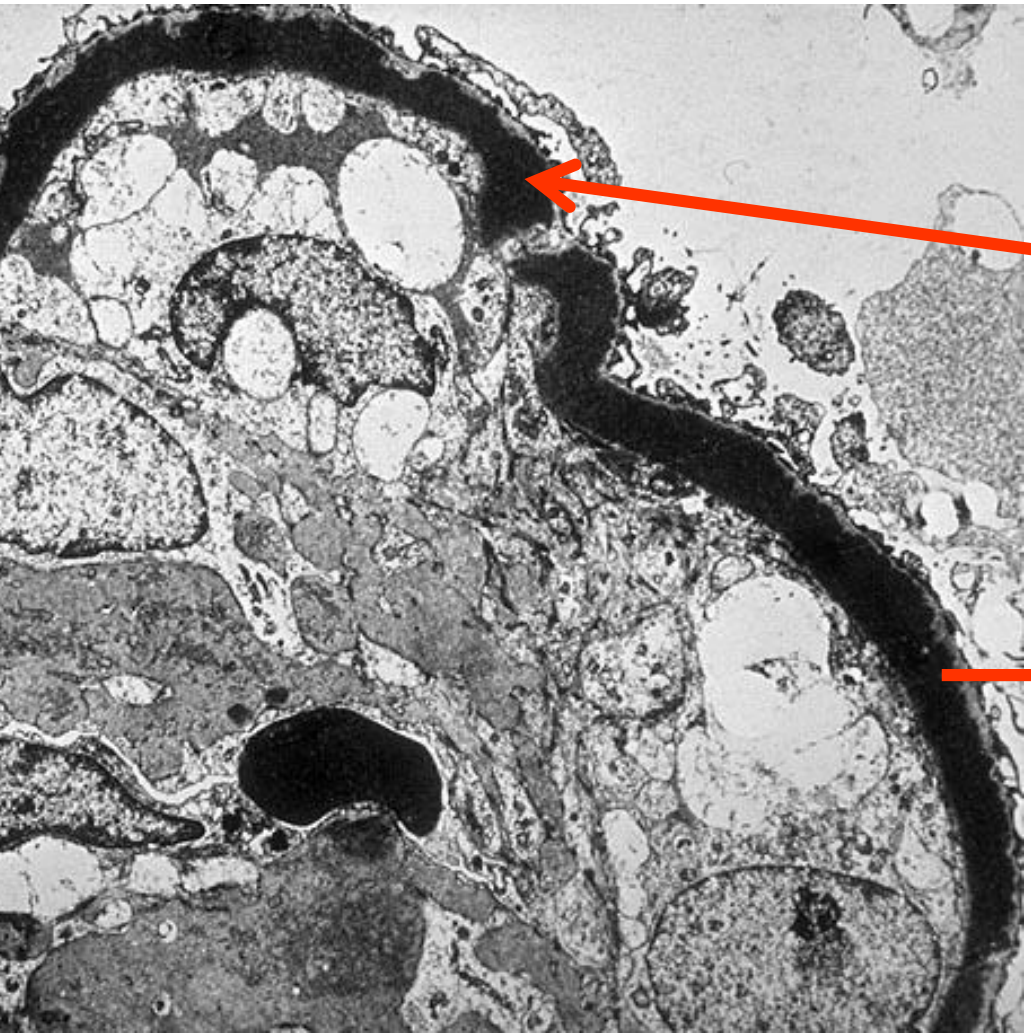
# Het filter in Dense Deposit Disease



Dense Deposit

=

C3

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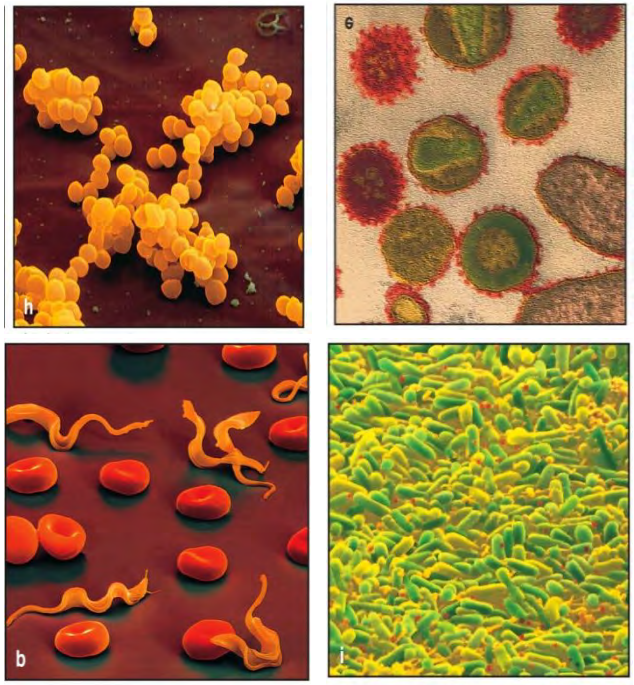
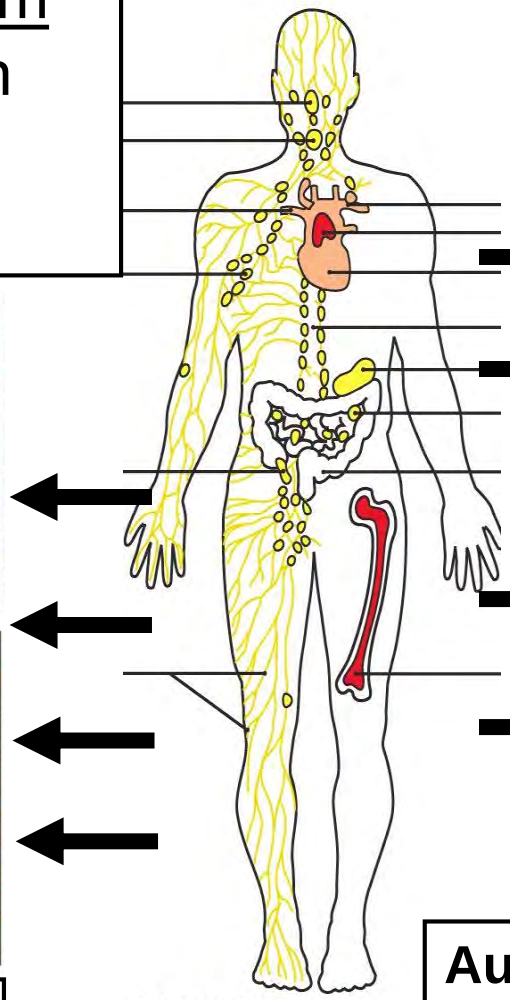
# Functies van het immuunsysteem

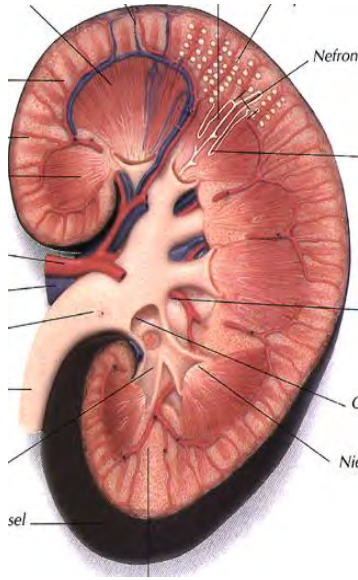
**Immuunsysteem**
Witte bloedcellen
Antistoffen
Complement

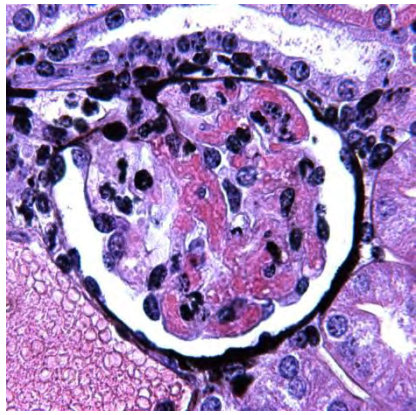


**Infecties**




**Orgaan**



**Autoimmuniteit**

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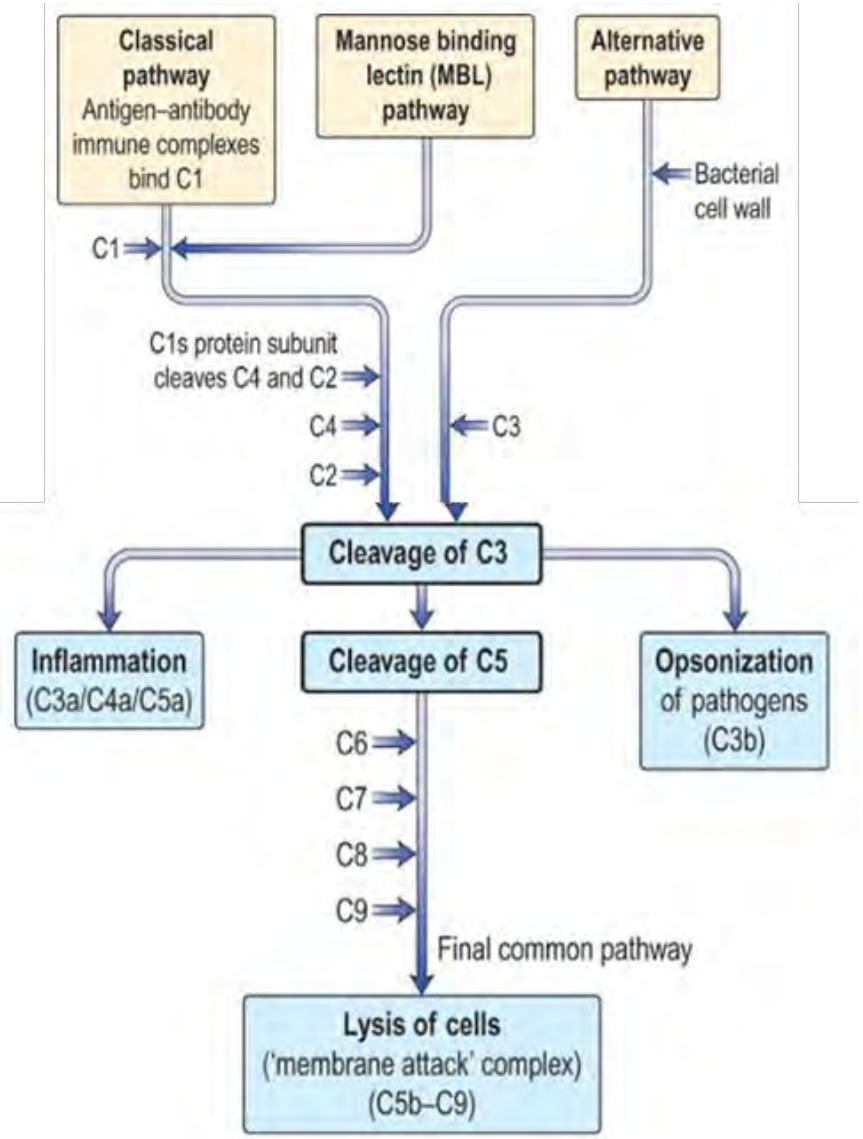
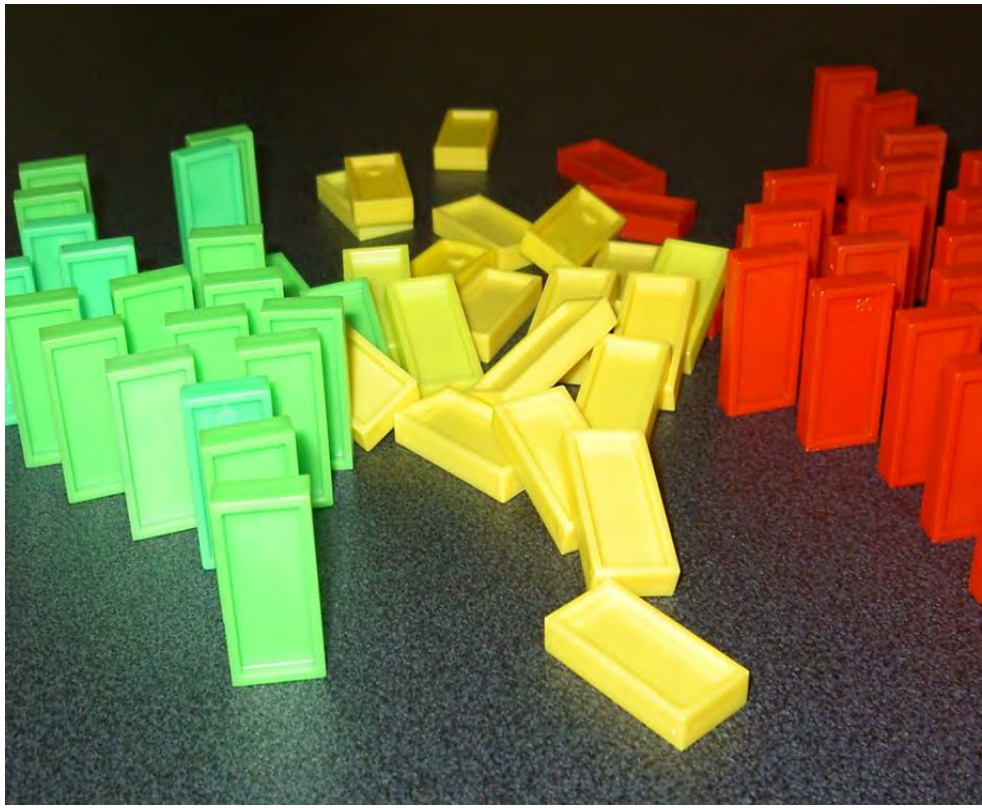
# De kettingreactie van complement activatie



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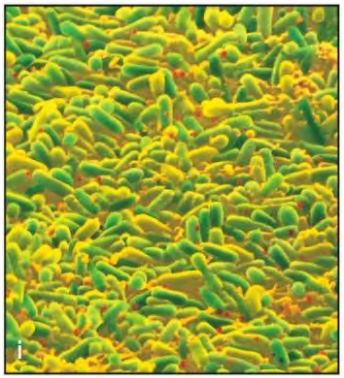
# De kettingreactie van complement activatie



1) Het opstarten van de complement reactie
    1) Klassieke route
    2) Lectine route
    3) Alternatieve route

2) Het versterken van de reactie
    1) Alternatieve route

3) De effecten
    1) Lysis / schade
    2) Ontsteking

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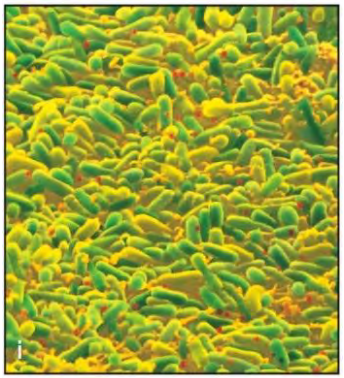
# Alternatieve Route van complement ‘activatie en remming’



Klassieke route

Lectine route

\+

Alternatieve route

C3

C5

Terminale route

# Alternatieve Route van complement
# ‘de motor van het complement systeem’

Klassieke route

Lectine route

+

Alternatieve route

C3

C5

Terminale route

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# Alternatieve Route van complement
# ‘de motor van het complement systeem’

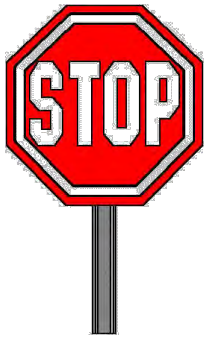
Klassieke route

Lectine route


Factor H, MCP, …

\+

Alternatieve route




C3

C5

Terminale route

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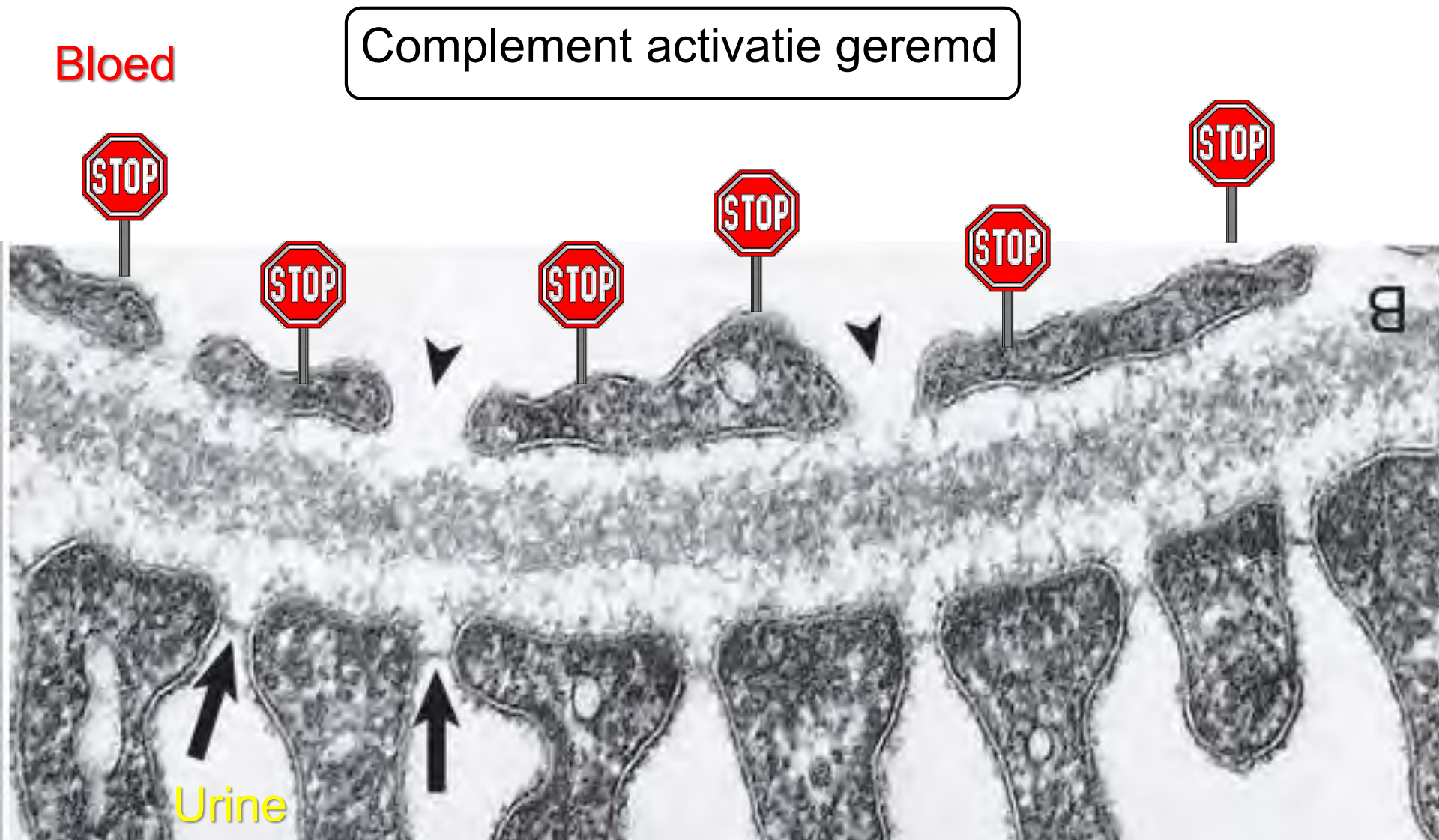
# Bescherming van de nier tegen complement activatie



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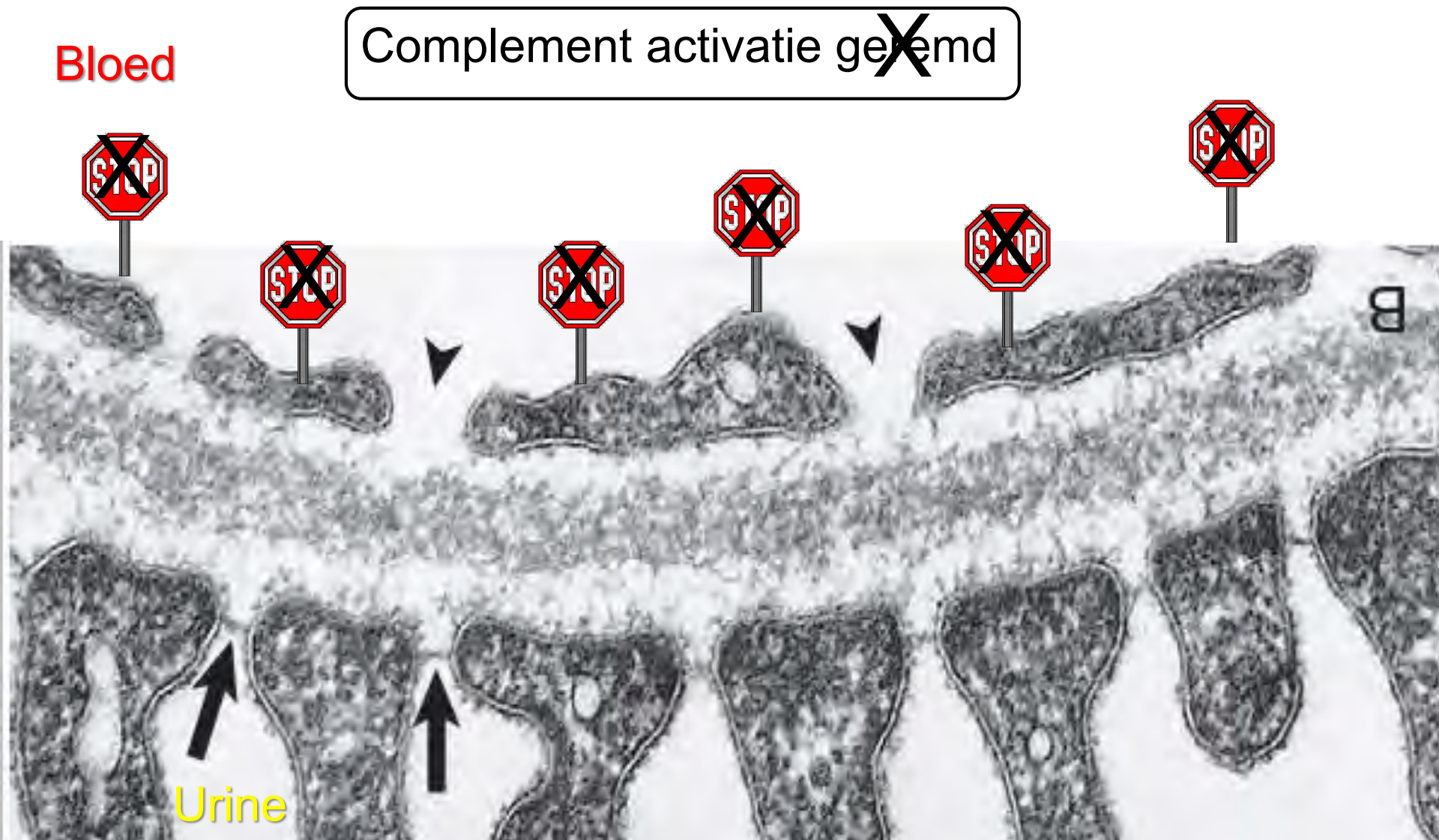
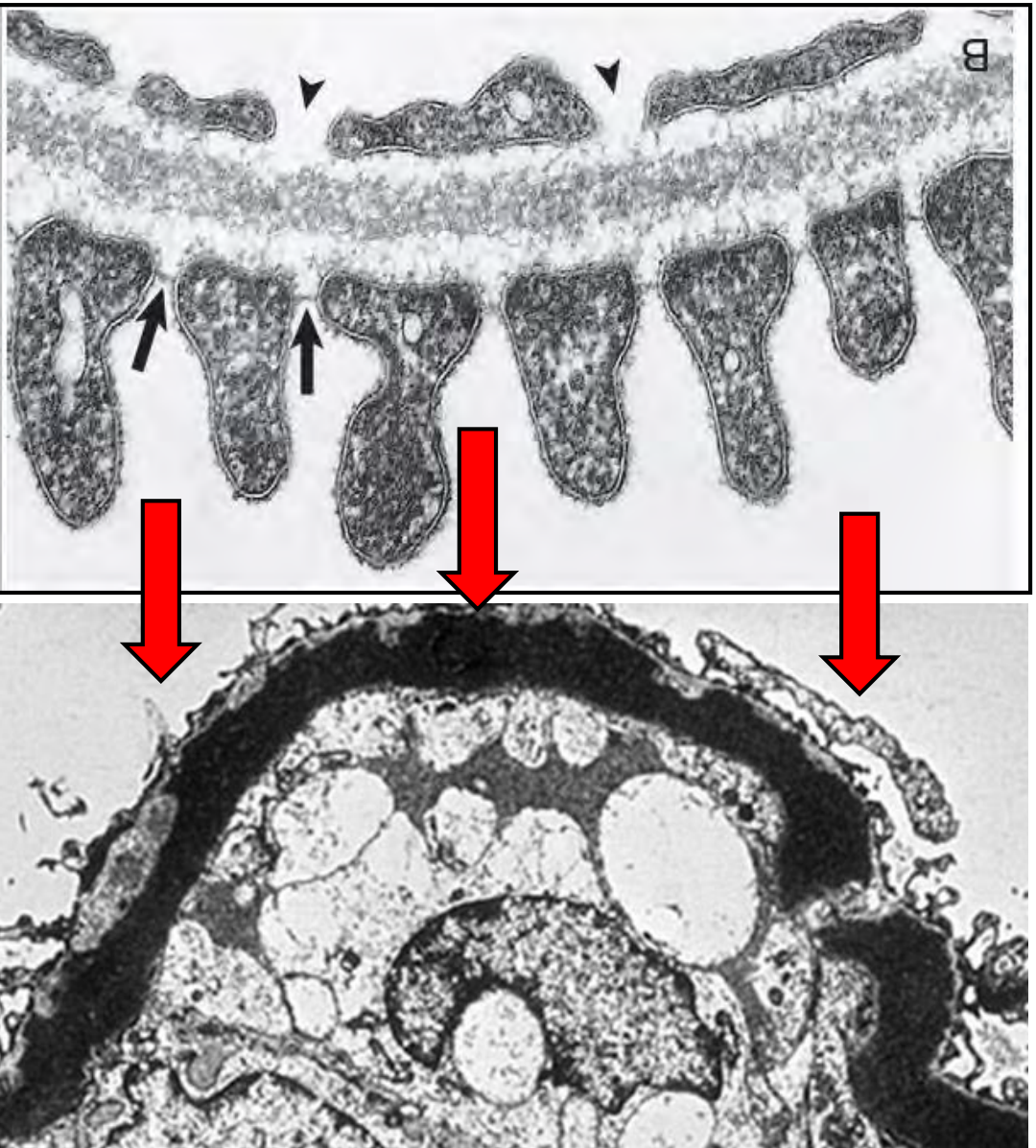


# Nierschade door complement



Het Filter

Verstopt = geen functie
Kapot = eiwit lek

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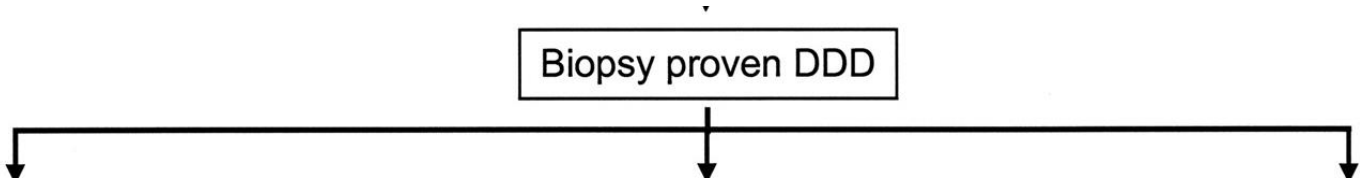
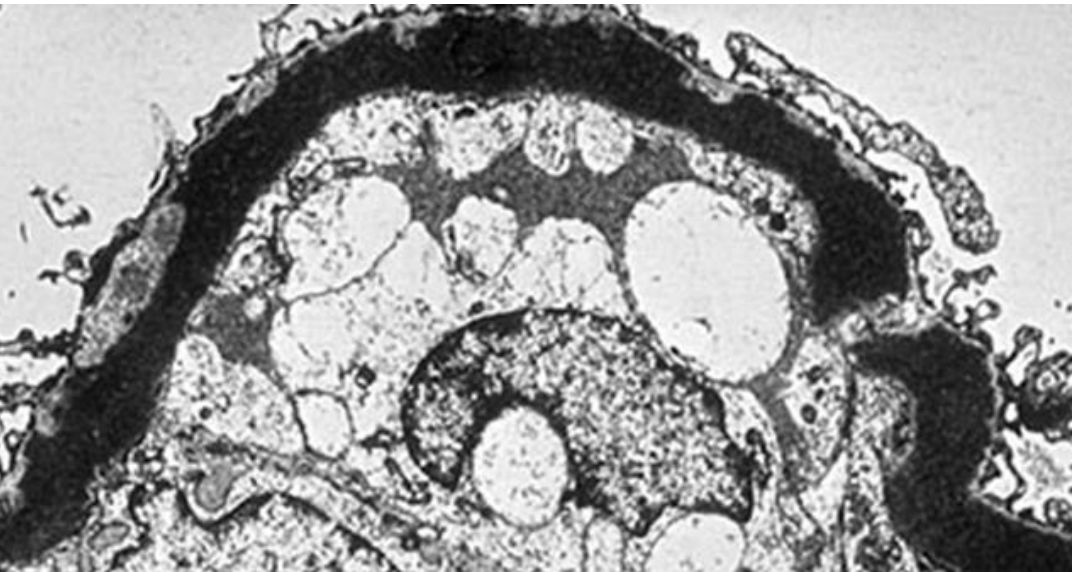
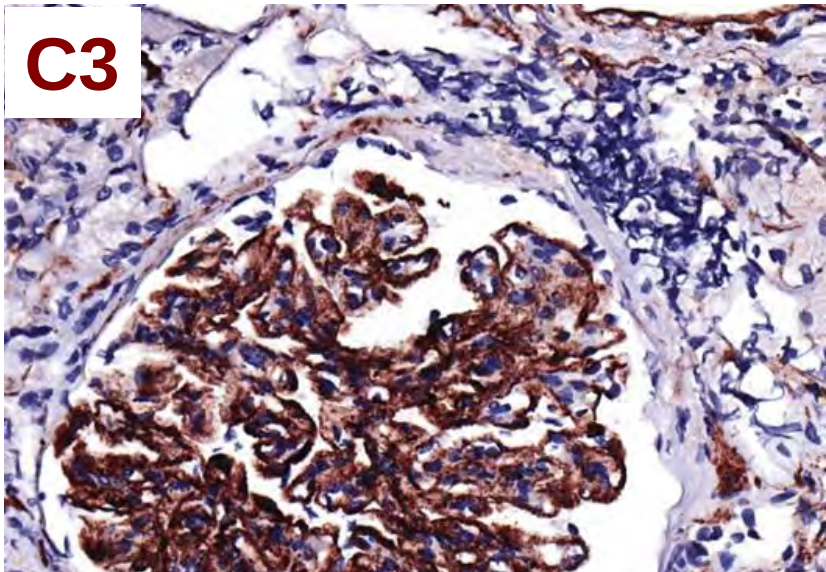
# Dense Deposit Disease - Diagnostiek

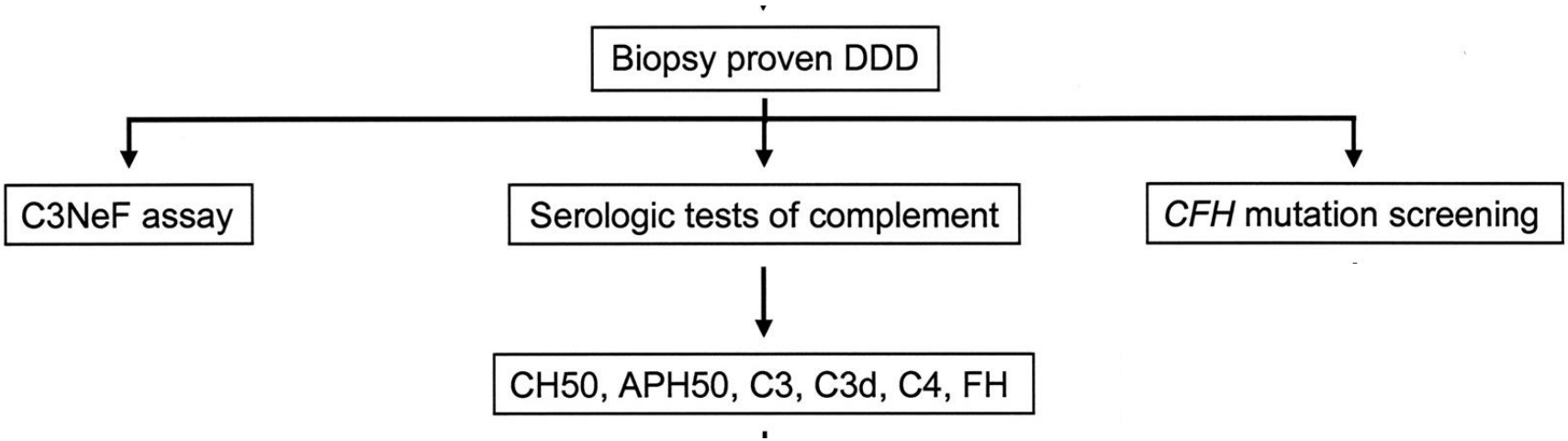



De gouden standaard





# Dense Deposit Disease - Diagnostiek

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# Dense Deposit Disease - Diagnostiek

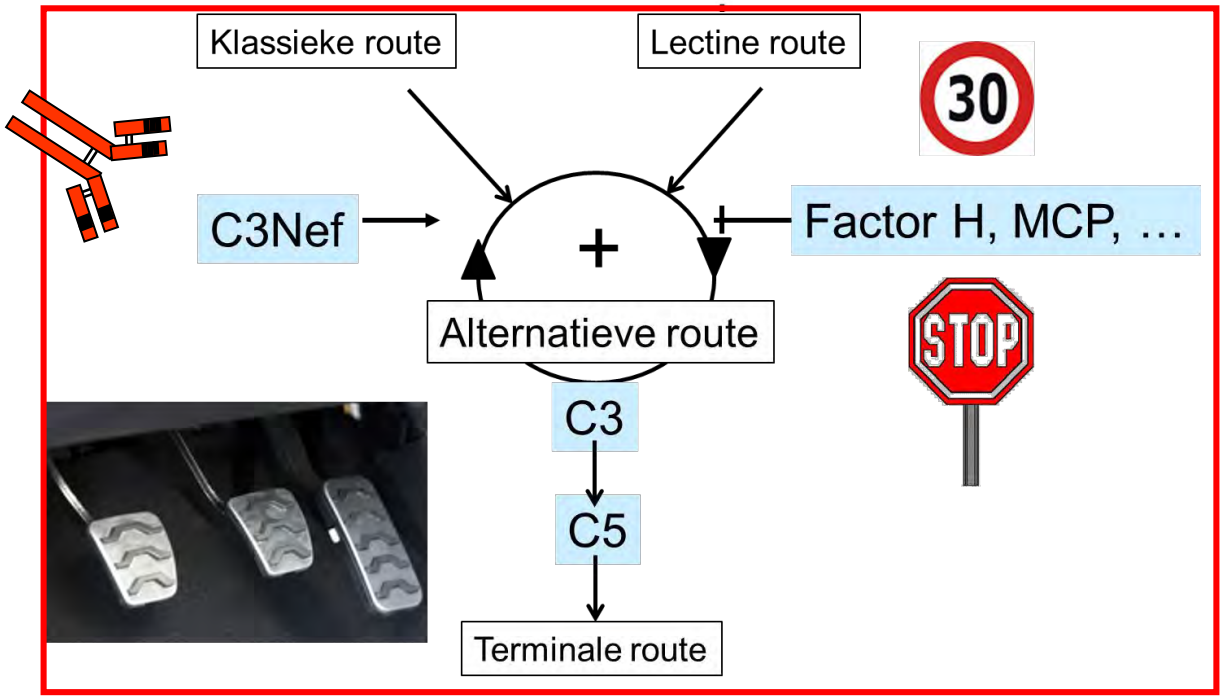
Biopsy proven DDD

C3NeF assay

Serologic tests of complement

*CFH* mutation screening

CH50, APH50, C3, C3d, C4, FH

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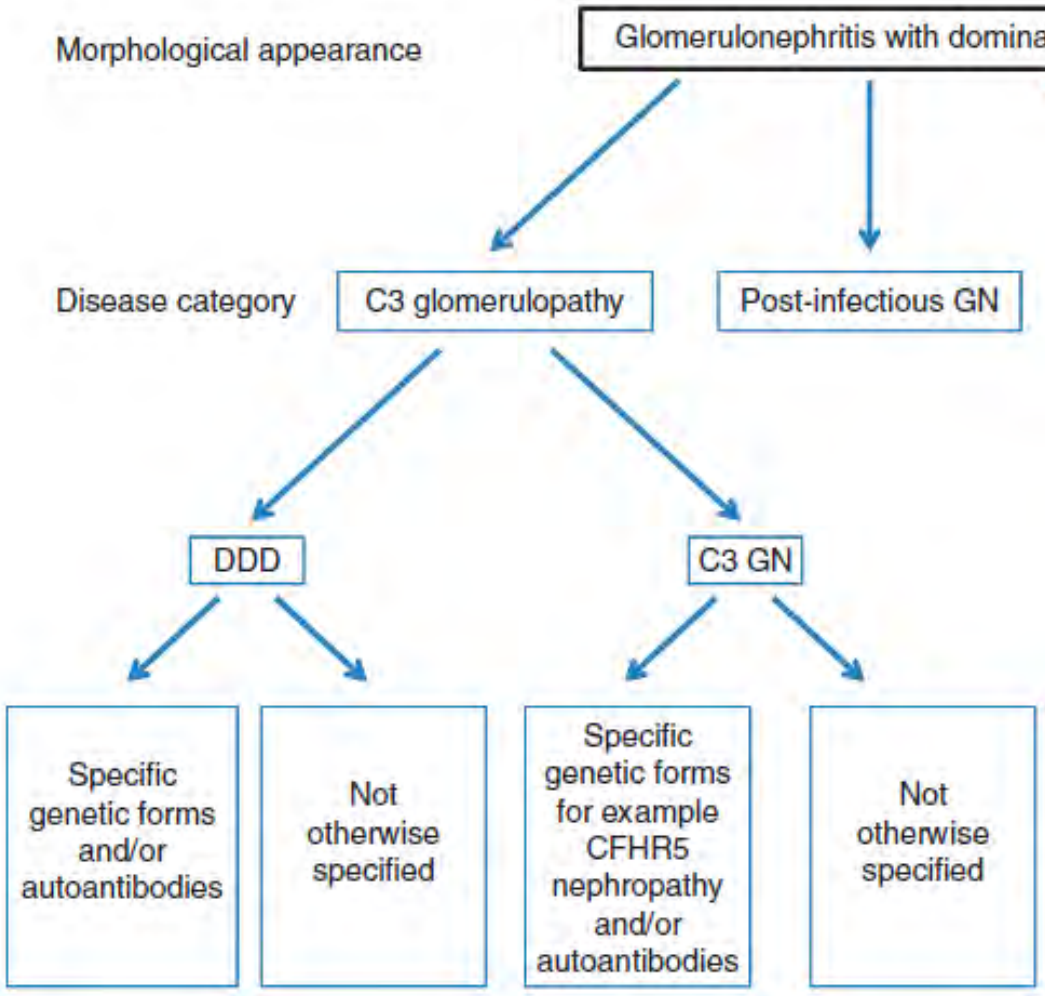
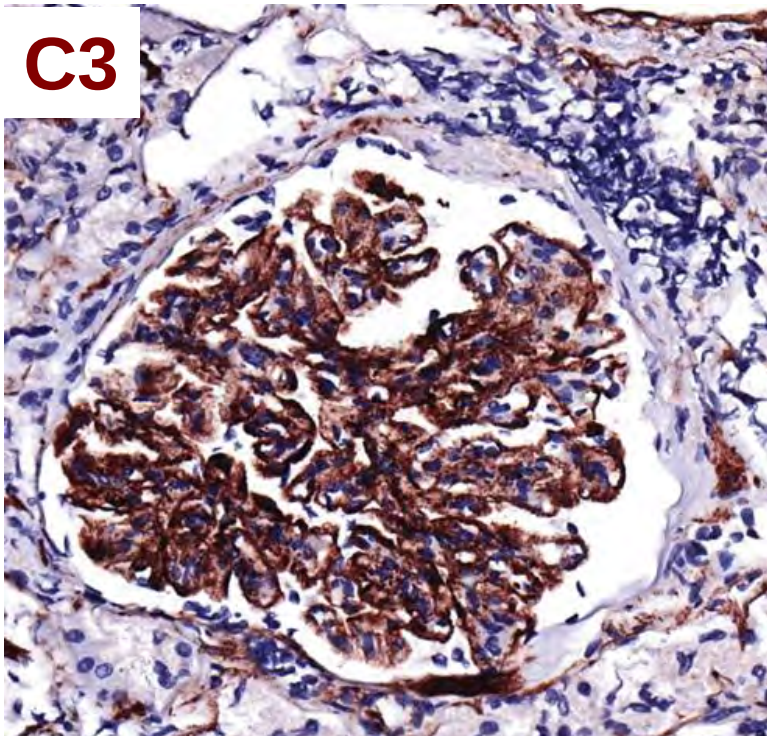
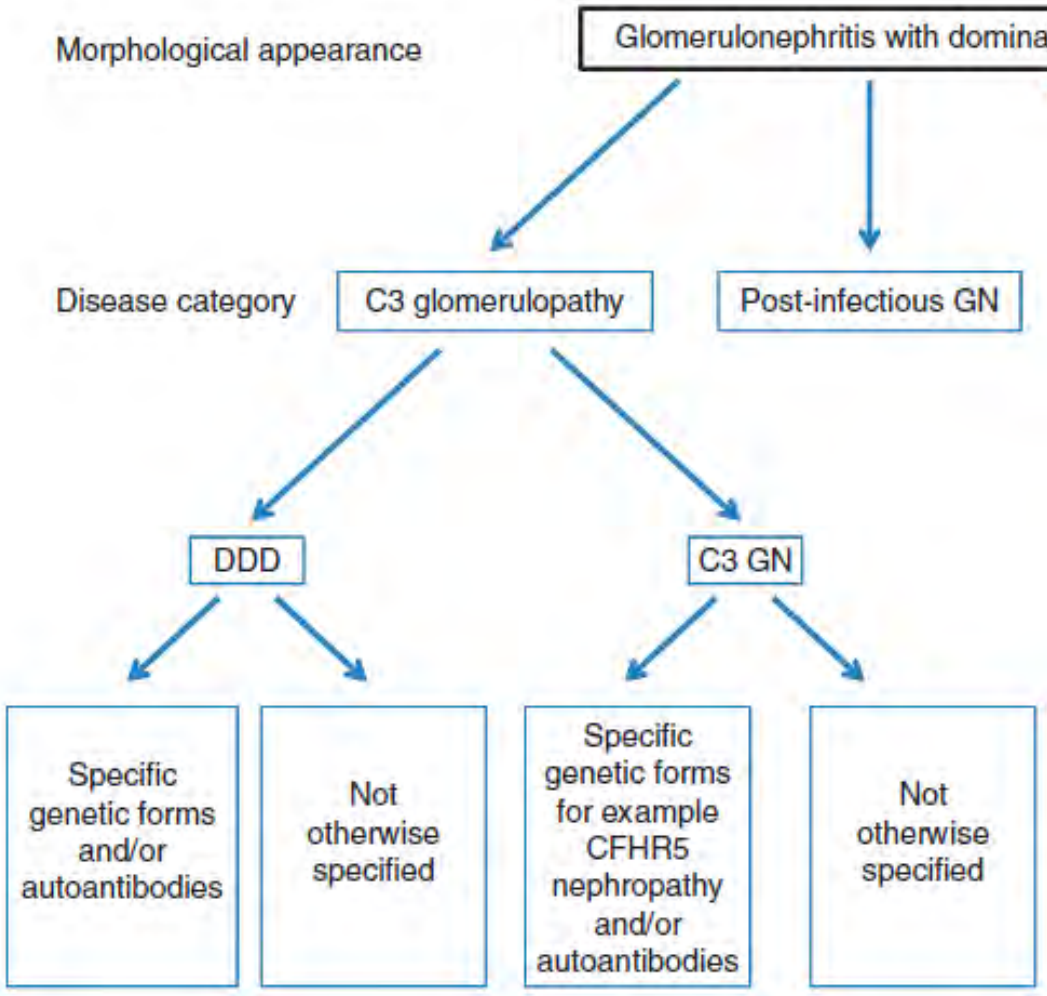
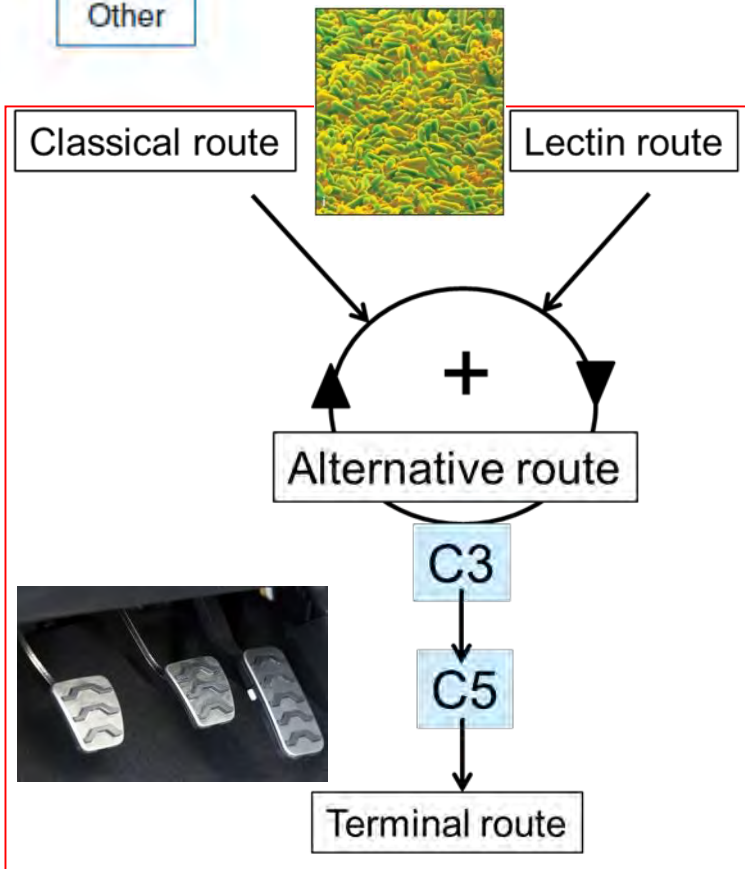
# Nieuwe indeling van DDD - C3 glomerulopathie



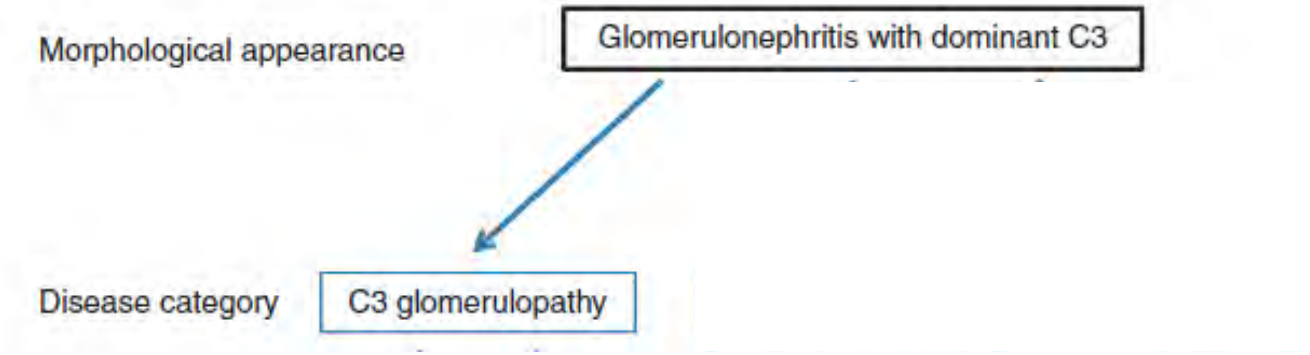



# Nieuwe indeling van DDD - C3 glomerulopathie



# Nieuwe indeling van DDD - C3 glomerulopathie




-ultra zeldzame ziekte (DDD 2-3 / miljoen / jaar)
-diagnose meestal op jonge leeftijd
-maar eerste presentatie kan ook op volwassen leeftijd
-overlap met andere ziektebeelden
-verschillende naam / inzichten – historische data gecompliceerd
-prognose 50% heeft na 10 jaar nierfalen
-na transplantatie grote kans op terugkeer van de ziekte

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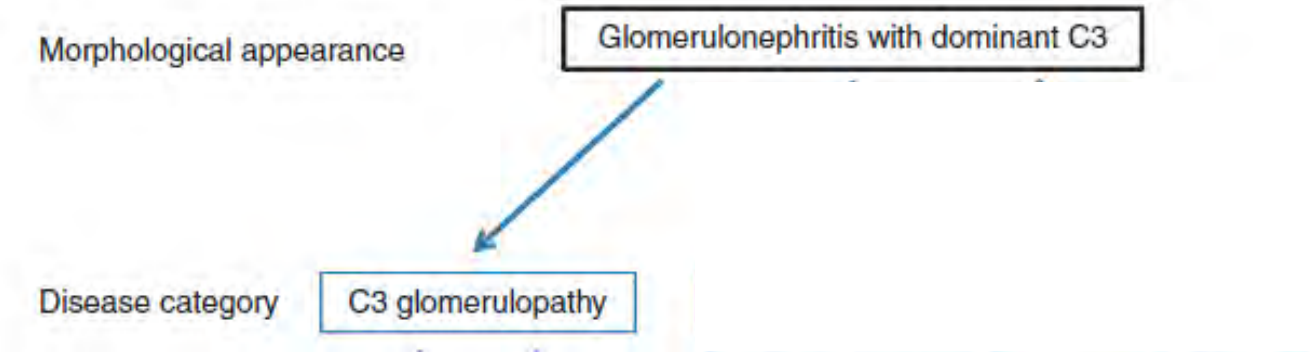
# Nieuwe indeling van DDD - C3 glomerulopathie

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Behandeling : Dr Darius Soonawala

NIERSTICHTING COMBAT CONSORTIUM


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# C3 glomerulopathy consensus report & KDIGO

Pickering et al Kidney Int 2013; Goodship et al Kidney Int 2017

http://www.kidney-international.org meeting report



OPEN

## C3 glomerulopathy: consensus report

2013

Matthew C. Pickering[1], Vivette D. D'Agati[2], Carla M. Nester[3,4], Richard J. Smith[3,4], Mark Haas[5], Gerald B. Appel[6], Charles E. Alpers[7], Ingeborg M. Bajema[8], Camille Bedrosian[9], Michael Braun[10], Mittie Doyle[9], Fadi Fakhouri[11], Fernando C. Fervenza[12], Agnes B. Fogo[13], Véronique Frémeaux-Bacchi[14], Daniel P. Gale[15], Elena Goicoechea de Jorge[1], Gene Griffin[9], Claire L. Harris[16], V. Michael Holers[17], Sally Johnson[18], Peter J. Lavin[19], Nicholas Medjeral-Thomas[1], B. Paul Morgan[16], Cynthia C. Nast[5], Laure-Hélène Noel[20], D. Keith Peters[21], Santiago Rodríguez de Córdoba[22], Aude Servais[23], Sanjeev Sethi[24], Wen-Chao Song[25], Paul Tamburini[9], Joshua M. Thurman[17], Michael Zavros[26] and H. Terence Cook[1]

www.kidney-international.org meeting report

## Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference

2017

OPEN

Timothy H.J. Goodship[1], H. Terence Cook[2], Fadi Fakhouri[3], Fernando C. Fervenza[4], Véronique Frémeaux-Bacchi[5], David Kavanagh[1], Carla M. Nester[6,7], Marina Noris[8], Matthew C. Pickering[2], Santiago Rodríguez de Córdoba[9], Lubka T. Roumenina[10,11,12], Sanjeev Sethi[13] and Richard J.H. Smith[6,7]; for Conference Participants[14]

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# Diagnostiek en follow up testen

## 1 Testen voor alle patienten

*Tests recommended in all patients*

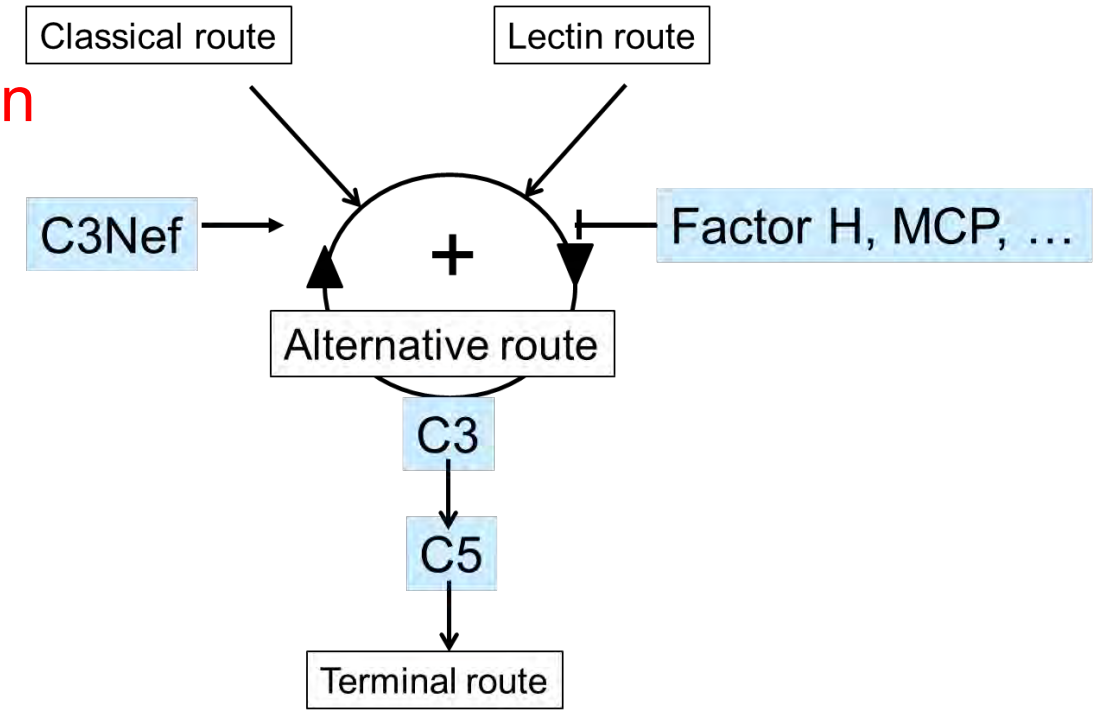
Measurement of serum C3 and C4

Measurement of C3 nephritic factor

Measurement of serum factor H

Serum paraprotein detection

Screening for *CFHR5* mutation



# Diagnostiek en follow up testen

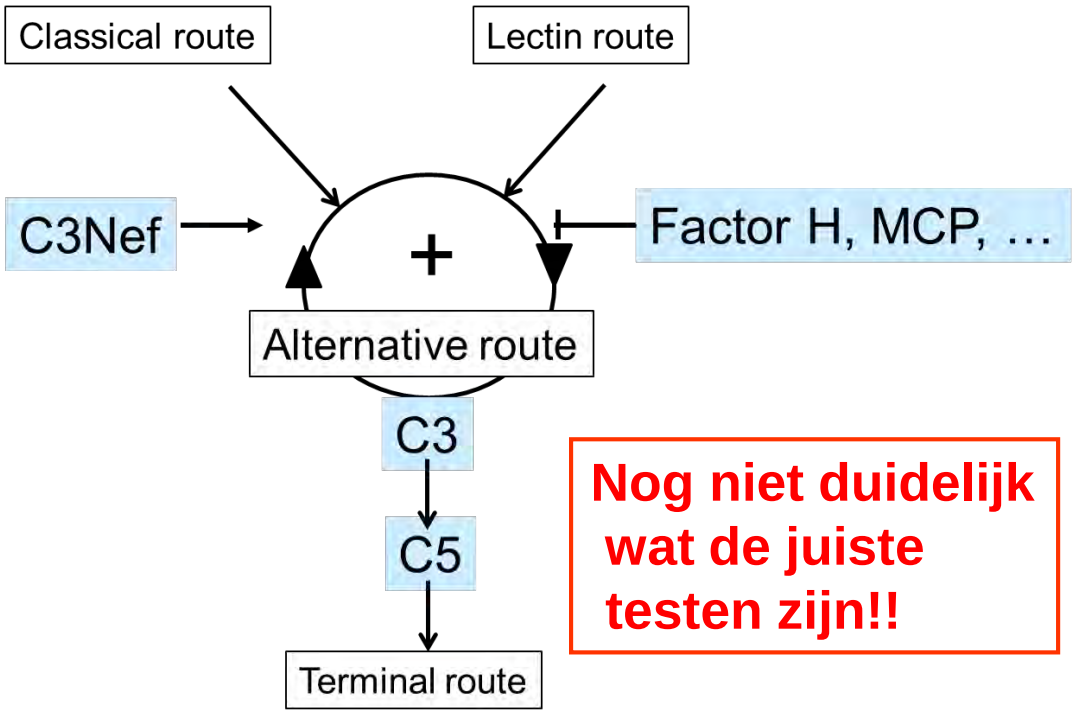
**2 Testen voor sommige patienten die een expert nodig hebben voor interpretatie en klinische betekenis**

Measurement of serum factor B

Measurement of serum C5

Measurement of markers of C3 activation, e.g., C3d, C3c, C3adesArg
Measurement of markers of C5 activation, e.g., C5adesArg, soluble C5b-9
Measurement of anti-factor H autoantibodies

Anti-factor B autoantibodies




**Nog niet duidelijk wat de juiste testen zijn!!**

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## C3G Satellite Meeting
## Friday, September 8th 2017, Copenhagen, Denmark

**VENUE:** Hotel Scandic Copenhagen, Vester Søgade 6, 1601 Copenhagen, Denmark
5 minutes' walk from Copenhagen Central Station

**8:20-9:25**
**Renal Pathology: What it does and does not tell us**
**Facilitator**: Matthew Pickering

**9:25-10:30**
**Biomarkers and Mechanisms**
**Facilitator**: Marina Noris

**13:15-14:45**
**Clinical Phenotype: Challenges and messages from the clinic**
**Facilitator**: Gerald Appel

**15:00-17:00**
**Treatment Strategies**
**Facilitator**: Richard Smith

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# COMBAT

Jaap van den Born
UMCG

Cees van Kooten
LUMC

Marc Seelen
UMCG

Nicole van de Kar
RadmoudMC

Bert van den Heuvel
RadboudMC

Piet Gros
UU

Aiko de Vries
LUMC

Stefan Berger
UMCG

# Het COMBAT consortium

*patient verdacht van complement-gemedieerde nierziekte*

aHUS / G3G / transplantaat afstoting

## Juiste diagnose

- Genetische analyse: welke mutaties
- Weefsel analyse: complement in weefsel
- Functionele analyse: nieuwe en bestaande assays om complement in serum te meten optimaliseren en nationaal met elkaar afstemmen


## Juiste therapie

- Effectiviteit van therapie vervolgen

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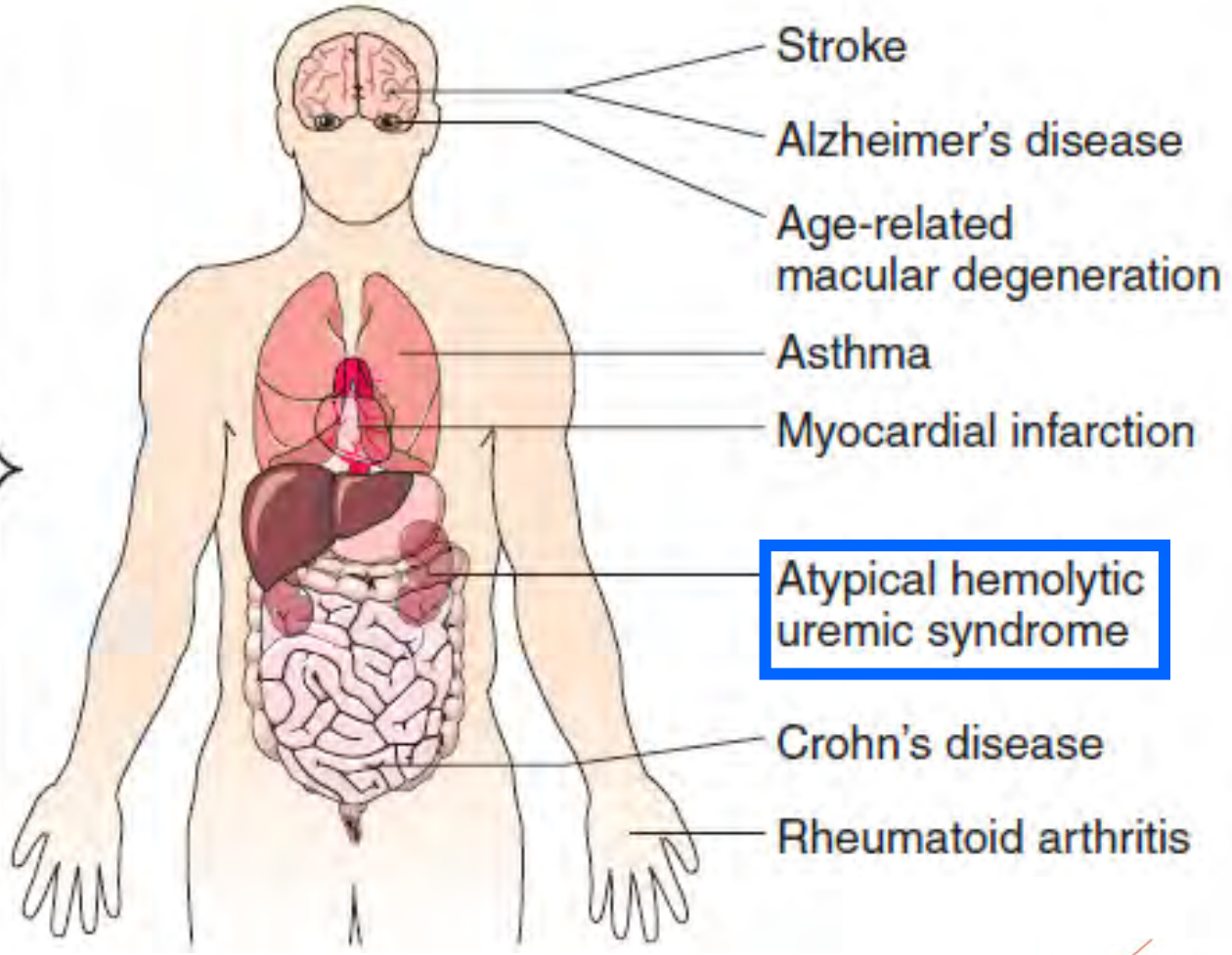
# Ziekten waar complement mogelijk een rol speelt
## *behandeling met Eculizumab*




**Ricklin & Lambris (2007) Nat Biotechn 25:1265**

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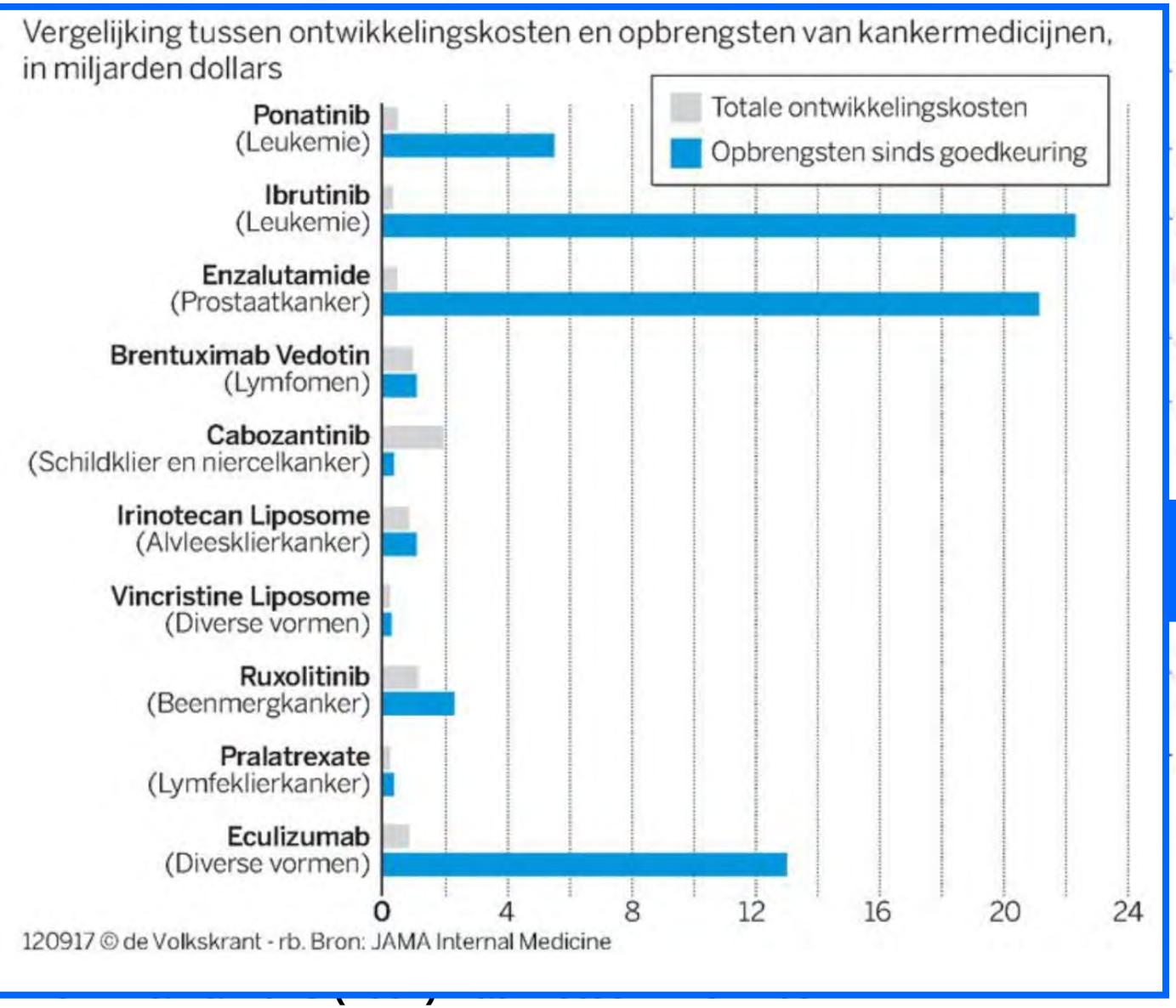
# Ziekten waar complement mogelijk een rol speelt
## *behandeling met Eculizumab*




- Stroke
- Alzheimer's disease
- Age-related macular degeneration
- Asthma
- Myocardial infarction
- **Atypical hemolytic uremic syndrome**
- Crohn's disease
- Rheumatoid arthritis

COMBAT NIERSTICHTING CONSORTIUM

# In kleine studies is het effect van Eculizumab in C3G/DDD onderzocht

## Eculizumab in Pediatric Dense Deposit Disease

*Michiel J.S. Oosterveld,* Mark R. Garrelfs,* Bernd Hoppe,† Sandrine Florquin,‡ Joris J.T.H. Roelofs,‡ L.P. van den Heuvel,§ Kerstin Amann,‖ Jean-Claude Davin,* Antonia H.M. Bouts,* Pietrik J. Schriemer,* and Jaap W. Groothoff**

Abstract

**Background and objectives** Dense deposit disease (DDD), a subtype of C3 glomerulopathy, is a rare disease affecting mostly children. Treatment options are limited. Debate exists whether eculizumab, a monoclonal antibody against complement factor C5, is effective in DDD. Reported data are scarce, especially in children.

**Conclusions** In this case series of pediatric patients with DDD, eculizumab treatment was associated with reduction in proteinuria and increase in eGFR. Leukocyturia resolved within 1 week of initiation of eculizumab treatment. These results underscore the need for a randomized trial of eculizumab in DDD.

*Clin J Am Soc Nephrol* 10: 1773–1782, 2015. doi: 10.2215/CJN.01360215

COMBAT NIERSTICHTING CONSORTIUM

www.kidney-international.org meeting report

# Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference

OPEN

Timothy H.J. Goodship[1], H. Terence Cook[2], Fadi Fakhouri[3], Fernando C. Fervenza[4], Véronique Frémeaux-Bacchi[5], David Kavanagh[1], Carla M. Nester[6,7], Marina Noris[8], Matthew C. Pickering[2], Santiago Rodríguez de Córdoba[9], Lubka T. Roumenina[10,11,12], Sanjeev Sethi[13] and Richard J.H. Smith[6,7]; for Conference Participants[14]

2017

## Table 5 | Recommended treatment approach for C3G[a]

**All patients**

- Optimal blood pressure control (suggested blood pressure below the 90% in children and ≤120/80 mm Hg in adults)
  - Priority agents include angiotensin converting enzyme inhibitors and angiotensin receptor blockers
- Optimal nutrition for both normal growth in children and healthy weight in adults
- Lipid control

**Moderate disease**

**Description**

- Urine protein over 500 mg/24 h despite supportive therapy

*or*

- Moderate inflammation on renal biopsy

*or*

- Recent increase in serum creatinine suggesting risk for progressive disease

**Recommendation**

- Prednisone
- Mycophenolate mofetil

NIERSTICHTING COMBAT CONSORTIUM

www.kidney-international.org meeting report

# Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference

OPEN

Timothy H.J. Goodship[1], H. Terence Cook[2], Fadi Fakhouri[3], Fernando C. Fervenza[4], Véronique Frémeaux-Bacchi[5], David Kavanagh[1], Carla M. Nester[6,7], Marina Noris[8], Matthew C. Pickering[2], Santiago Rodríguez de Córdoba[9], Lubka T. Roumenina[10,11,12], Sanjeev Sethi[13] and Richard J.H. Smith[6,7]; for Conference Participants[14]

2017

**Severe disease**

**Description**

- Urine protein over 2000 mg/24 h despite immunosuppression and supportive therapy

*or*

- Severe inflammation represented by marked endo- or extracapillary proliferation with or without crescent formation despite immunosuppression and supportive therapy

*or*

- Increased serum creatinine suggesting risk for progressive disease at onset despite immunosuppression and supportive therapy

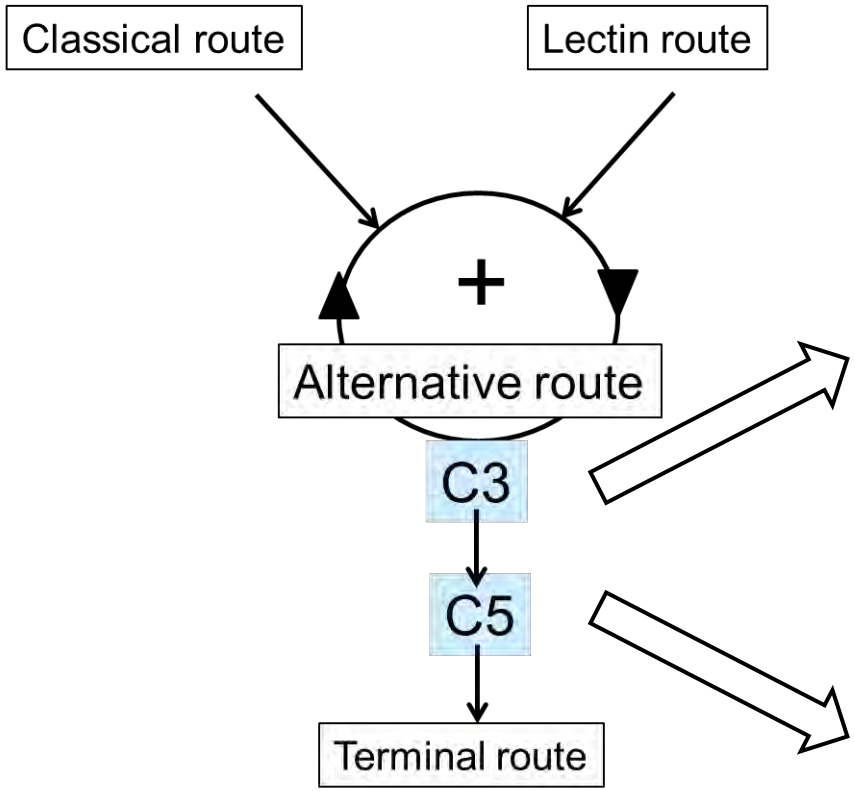
**Recommendation**

- Methylprednisolone pulse dosing as well as other anti-cellular immune suppressants have had limited success in rapidly progressive disease
- Data are insufficient to recommend eculizumab as a first-line agent for the treatment of rapidly progressive disease

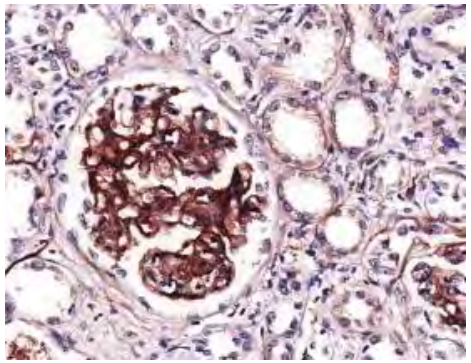
C3G, C3 glomerulopathy.
[a]Based on a single, small prospective trial, case reports, and expert opinion.

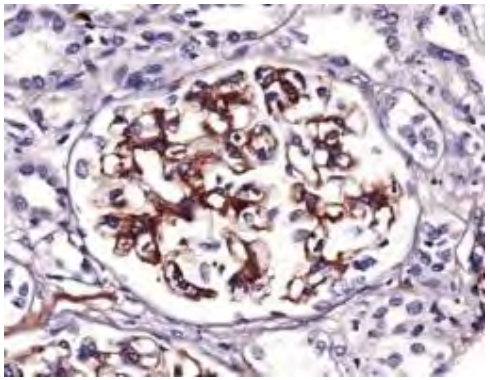
NIERSTICHTING COMBAT CONSORTIUM

# Kleuring voor complement in het nierbiopt

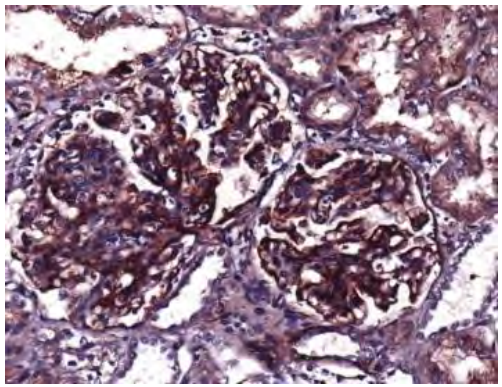


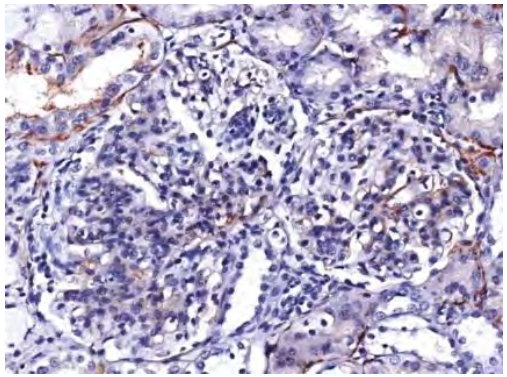

Pts 1





Pts 2





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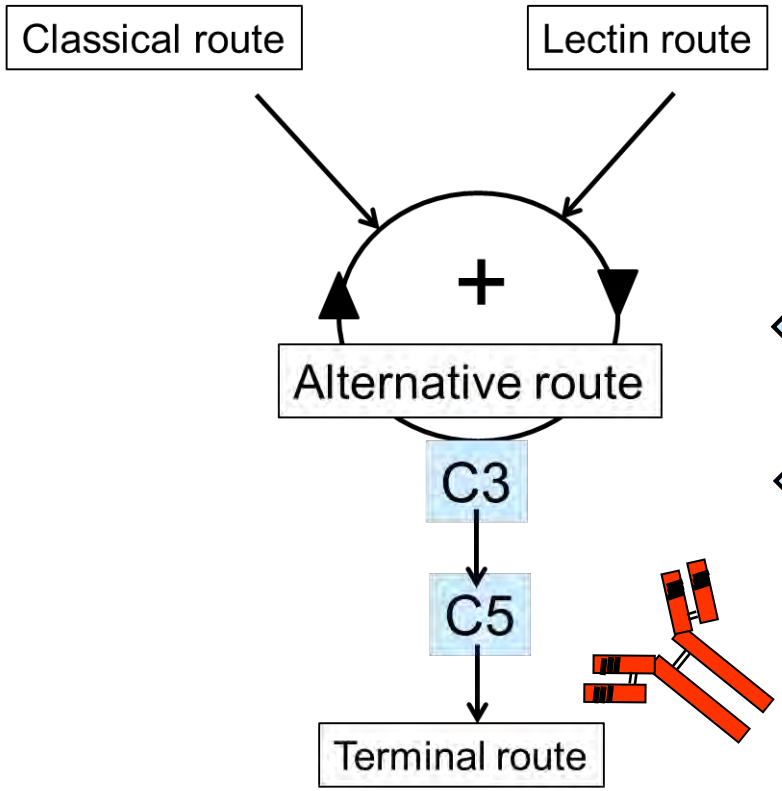
# Specifieke behandeling van C3G



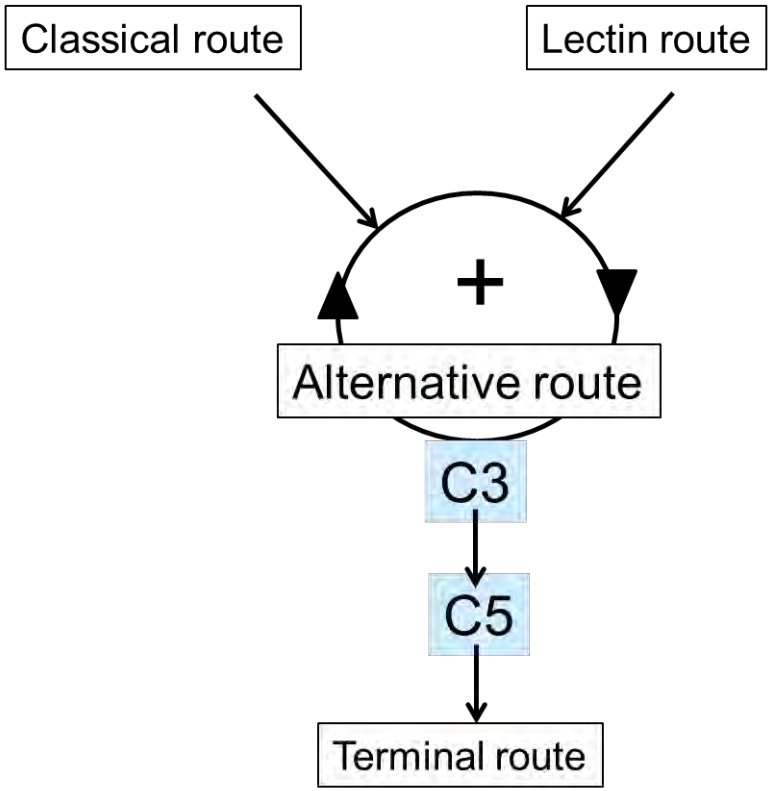

2. Nieuwe medicijnen (remmen C3 ipv C5)

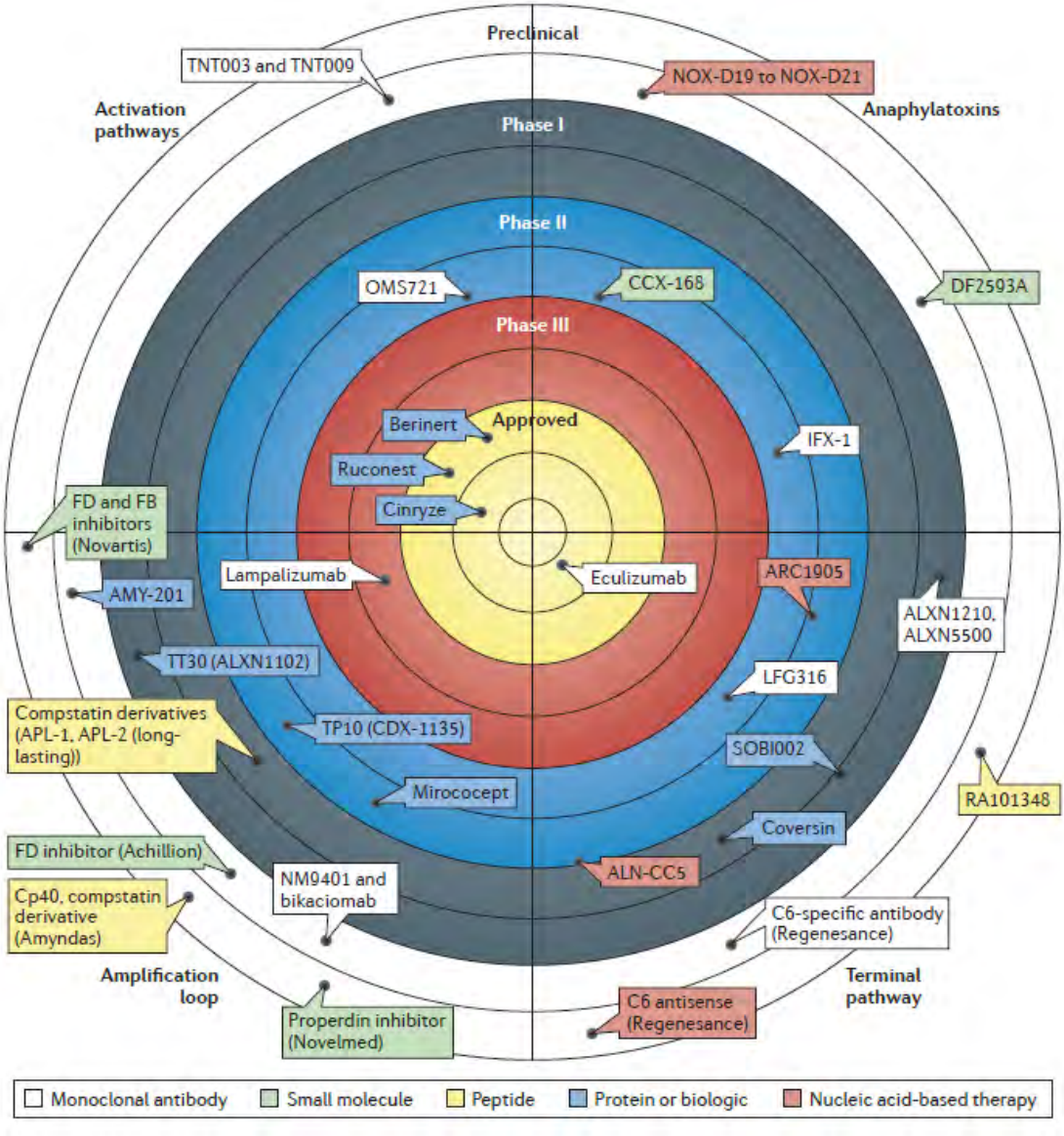
1. Betere Biomarkers

**Anti-C5 antibody ?**
**Eculizumab**

LUMC Nephrology

# Specifieke behandeling van C3G



**C3G Satellite Meeting**
**Friday, September 8th 2017, Copenhagen, Denmark**

**VENUE:** Hotel Scandic Copenhagen, Vester Søgade 6, 1601 Copenhagen, Denmark
5 minutes' walk from Copenhagen Central Station

| **15:00-17:00**<br>**Treatment Strategies**<br>**Facilitator**: Richard Smith | |
|---|---|
| When would we use eculizumab in C3G? | Gerald Appel |
| Targeting C3 | John Lambris (Amyndas) |
| Targeting factor D | Hetal Kocinsky (Achillion) |
| Targeting factor B | Anna Schubart (Novarits) |
| Targeting factor H and the FHR proteins | Peter Zipfel |
| Panel and Group Discussion | |
| | |

# Complement; twee kanten en steeds ingewikkelder

# Ontwikkelingen LUMC

- Expertise centrum voor C3G (volwassenen)
- Ontwikkelen van Zorgpad

- Opzetten registry (analogie met aHUS) – COMBAT
- Aansluiten bij internationale initiatieven
- Genetica en diagnostiek: Nijmegen, Sanquin,Iowa
- Nadruk op pathologie – diagnostiek – en biobank

- Klinische trials C3G

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Nephrology