What is C3 Glomerulopathy?

Goals – to understand…….

- What C3G is
- How the kidney works and that C3G affects the glomerulus
- That other diseases can look like C3G
- That C3G is caused by complement dysregulation
- What the complement system does
- How we study complement in individual patients
- The many causes of complement dysregulation
- That while there are no disease-specific treatment, the future is *very* bright and multiple new therapies are being tested in clinical trials

What is C3 Glomerulopathy?

- A group of rare kidney diseases characterized by
  - Complement dysregulation in the blood stream and in the kidney
  - We see a lot of complement C3 deposition in kidney biopsies
    - Required for diagnosis
- Two major subgroups with overlapping clinical and pathological features
  - Dense Deposit Disease (DDD)
  - C3 Glomerulonephritis (C3GN)

What is C3 Glomerulopathy?

- Underlying cause – dysregulation of complement
  - Dysregulation of the alternative pathway of the complement cascade
  - Dysregulation of the terminal pathway also common
- Dysregulation caused by
  - Autoantibodies usually targeting the C3 and/or C5 convertases
    - Called C3 nephritic factors or C3Nefs; C5 nephritic factors or C5Nefs
  - Disease drivers – genetic mutations less common (~20%)

What is C3 Glomerulopathy?

- No disease-specific treatments available
  - Immunosuppressive drugs and eculizumab (a terminal complement pathway blocker) are helpful in some patients
  - *However* no treatment universally effective or curative
  - Renal survival – about 10 years
- Transplantation as an option
  - High risk of disease recurrence (both DDD and C3GN)
- Clinical trials ongoing to test several first-generation drugs that target the alternative pathway – Carla Nester will discuss

You are here → Patient Presentation

Proteinuria, hematuria and other markers of glomerulonephritis and renal insufficiency with HTN +/- nephrotic syndrome

↓

Investigations

- **Blood tests; simple complement tests; urine tests**
- **Biopsy *if* persistent proteinuria >500mg/24hrs *and/or* unexplained HTN with hematuria**

Smith et al *Nature Reviews Nephrol* 2019

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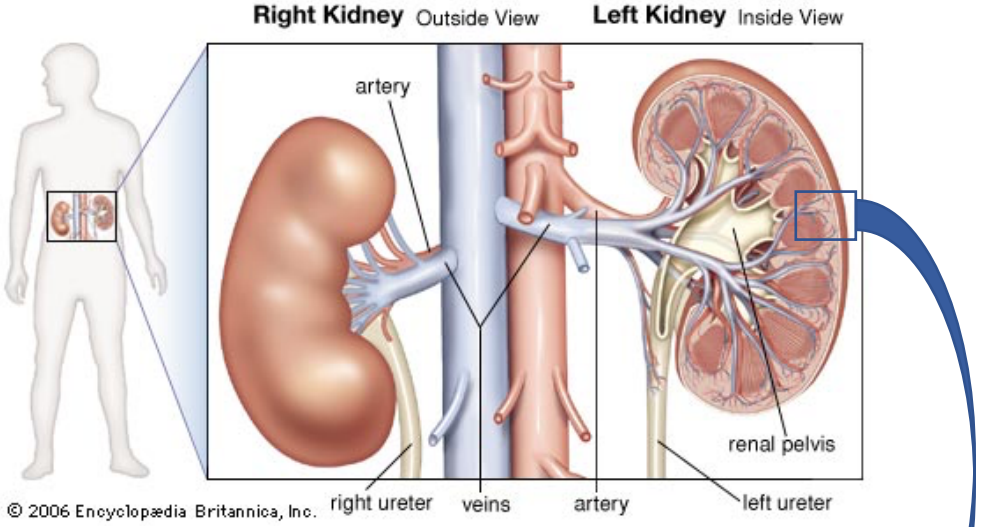
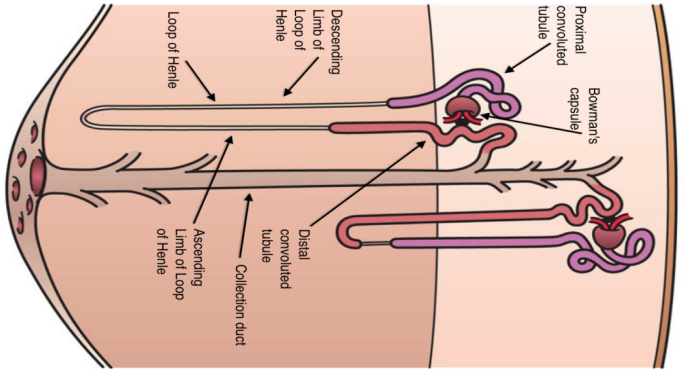
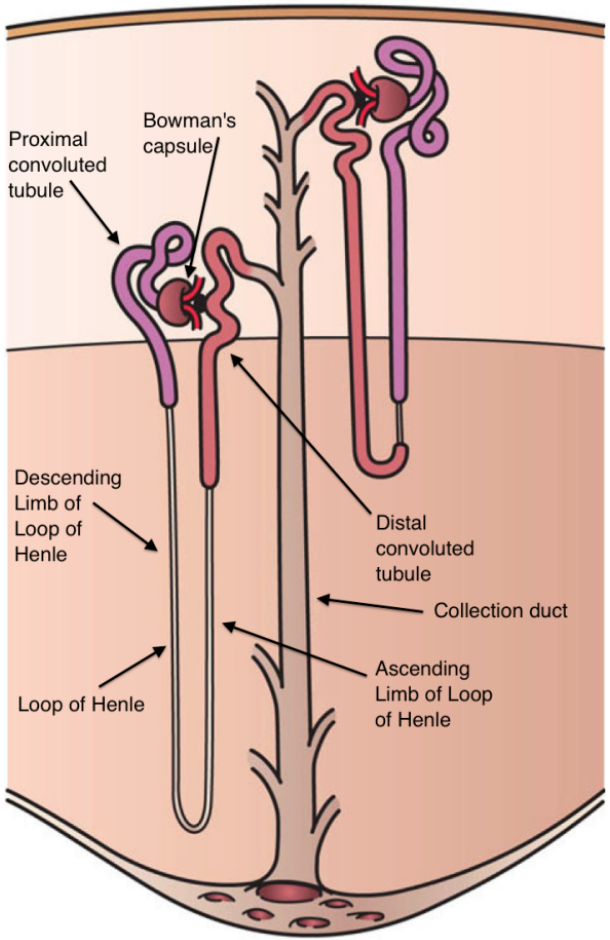
Biopsy-confirmed C3 Dominant GN

Smith et al *Nature Reviews Nephrol* 2019

Understanding the Kidney Biopsy

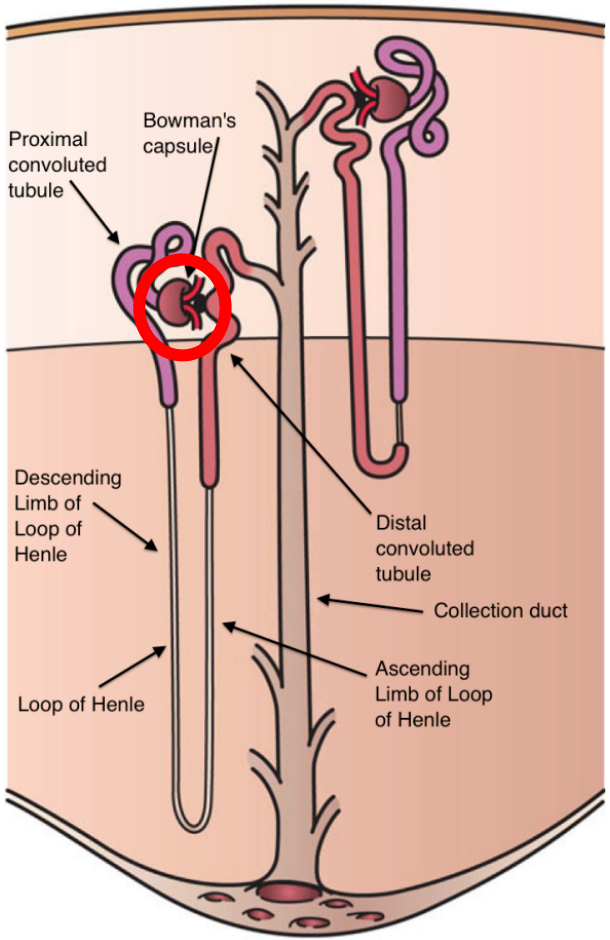


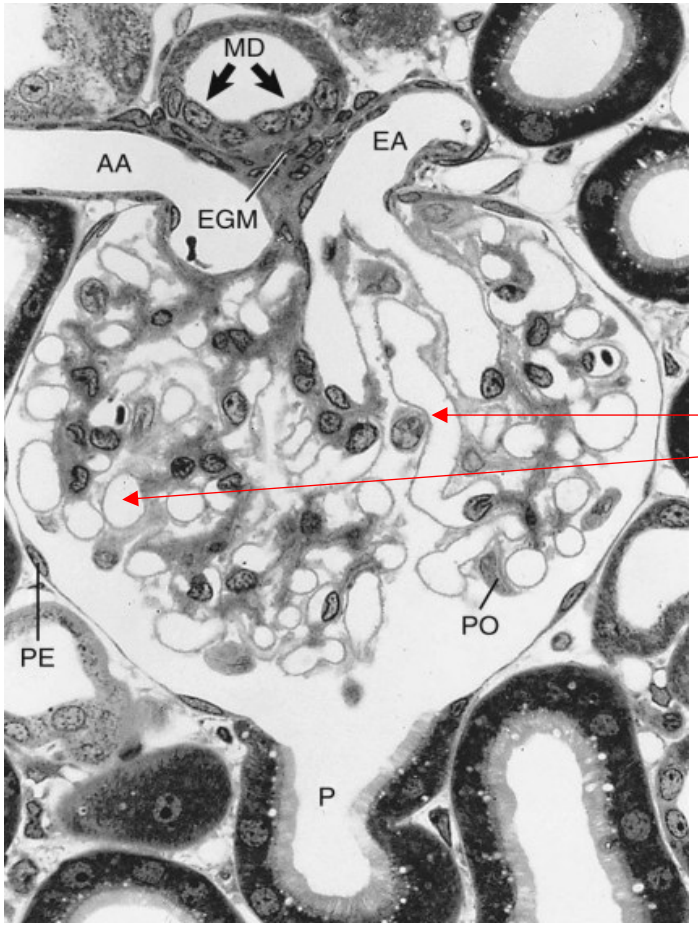




Nephron – the working unit of the kidney

For C3G we are interested in the glomerulus





Nephron – the working unit of the kidney

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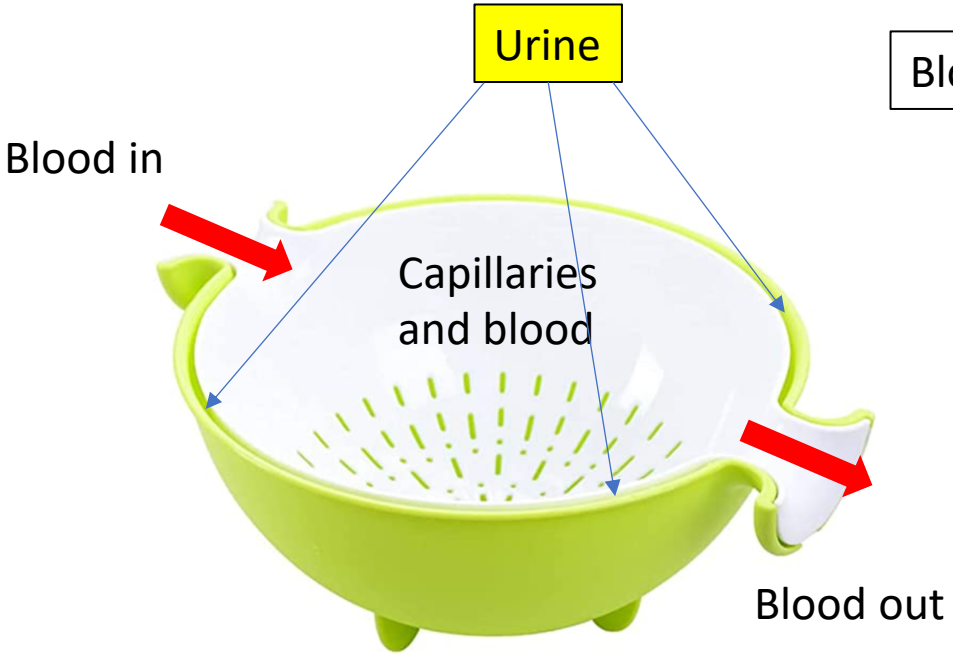
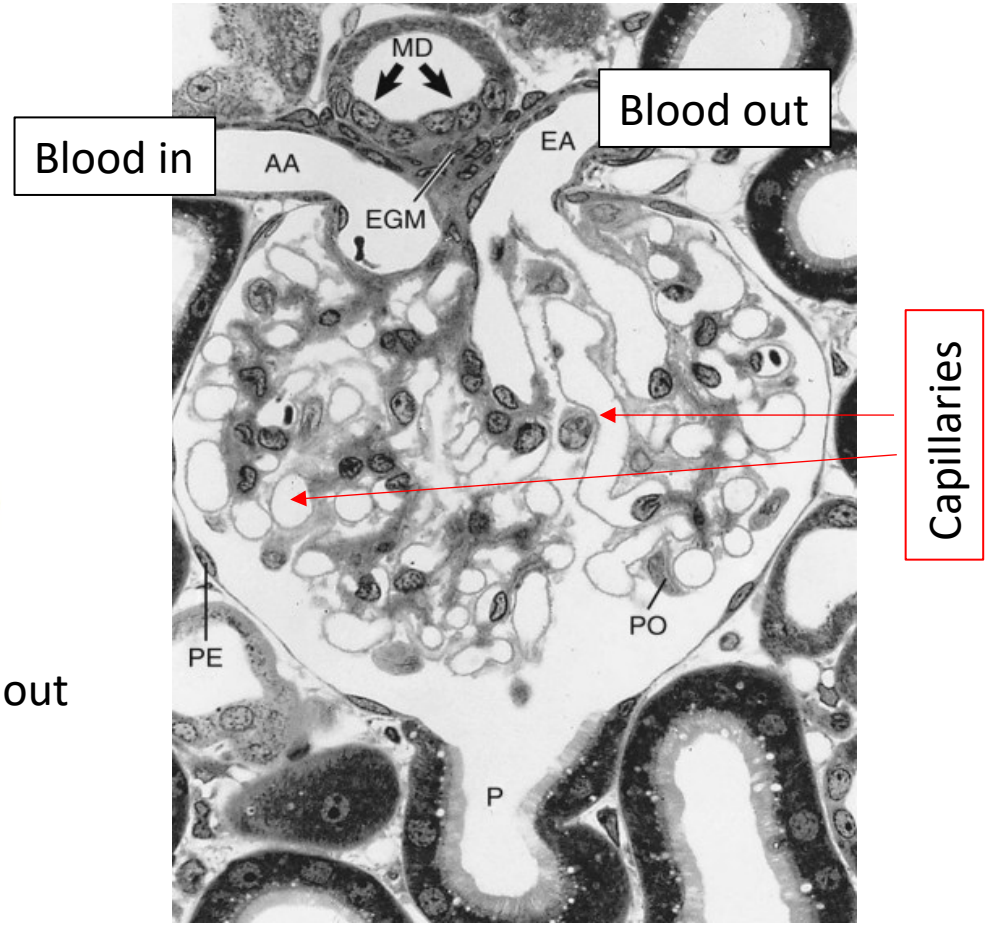
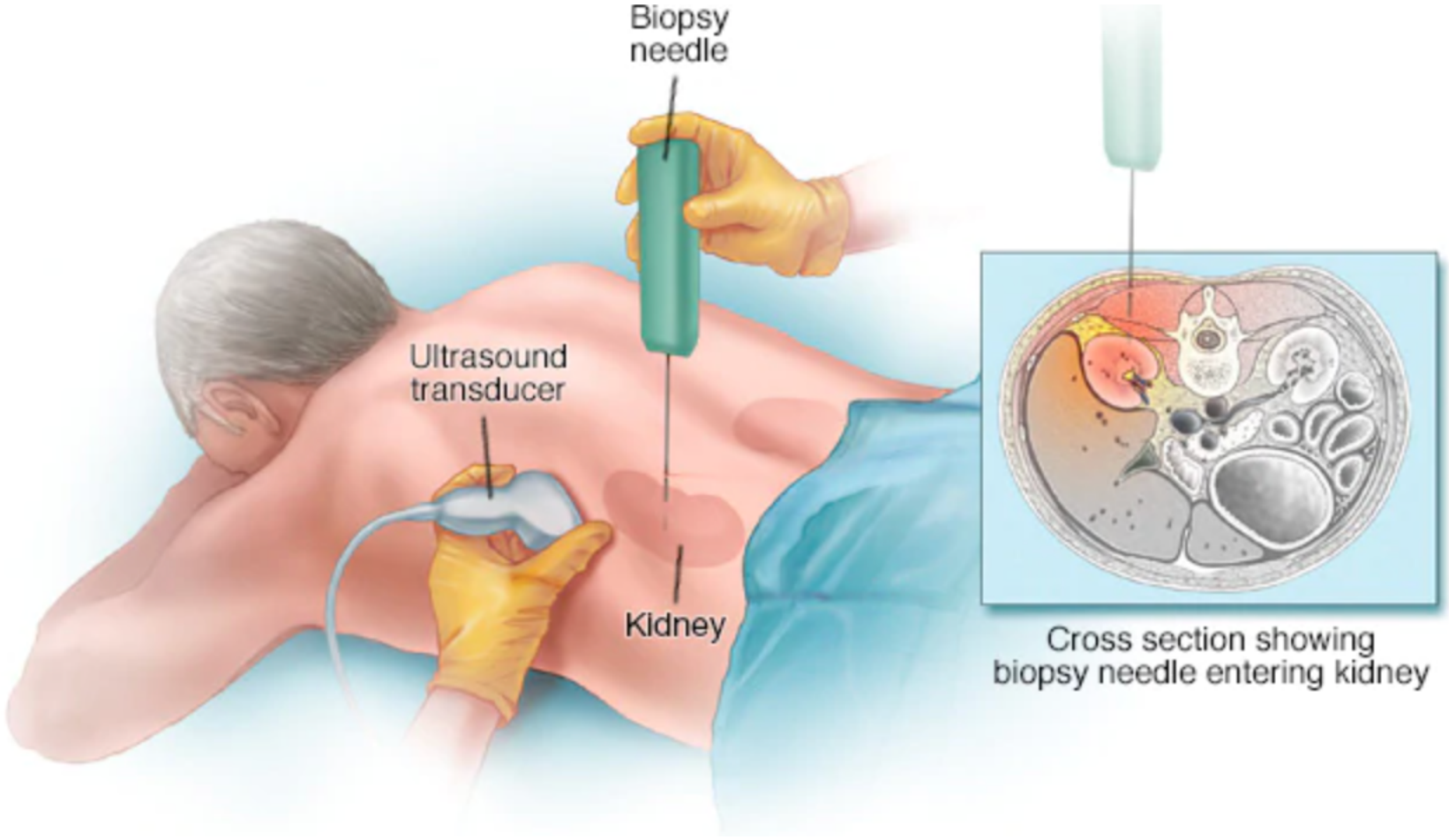
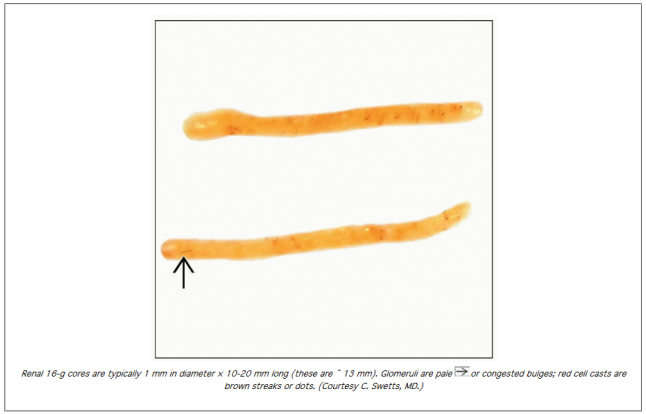


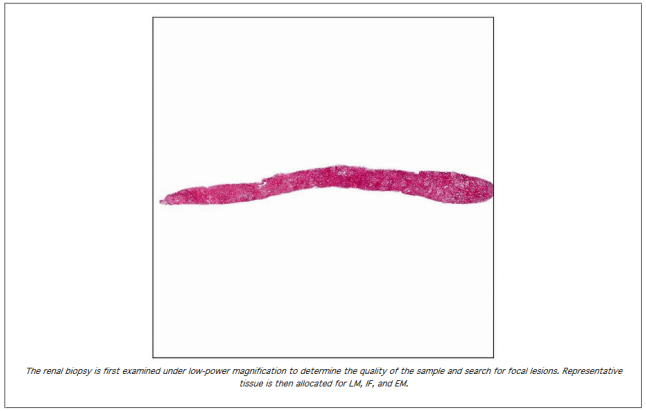



Biopsy needle
Ultrasound transducer
Kidney
Cross section showing biopsy needle entering kidney

About 1 mm x 20 mm



Renal 16-g cores are typically 1 mm in diameter × 10-20 mm long (these are ~ 13 mm). Glomeruli are pale or congested bulges; red cell casts are brown streaks or dots. (Courtesy C. Swetts, MD.)

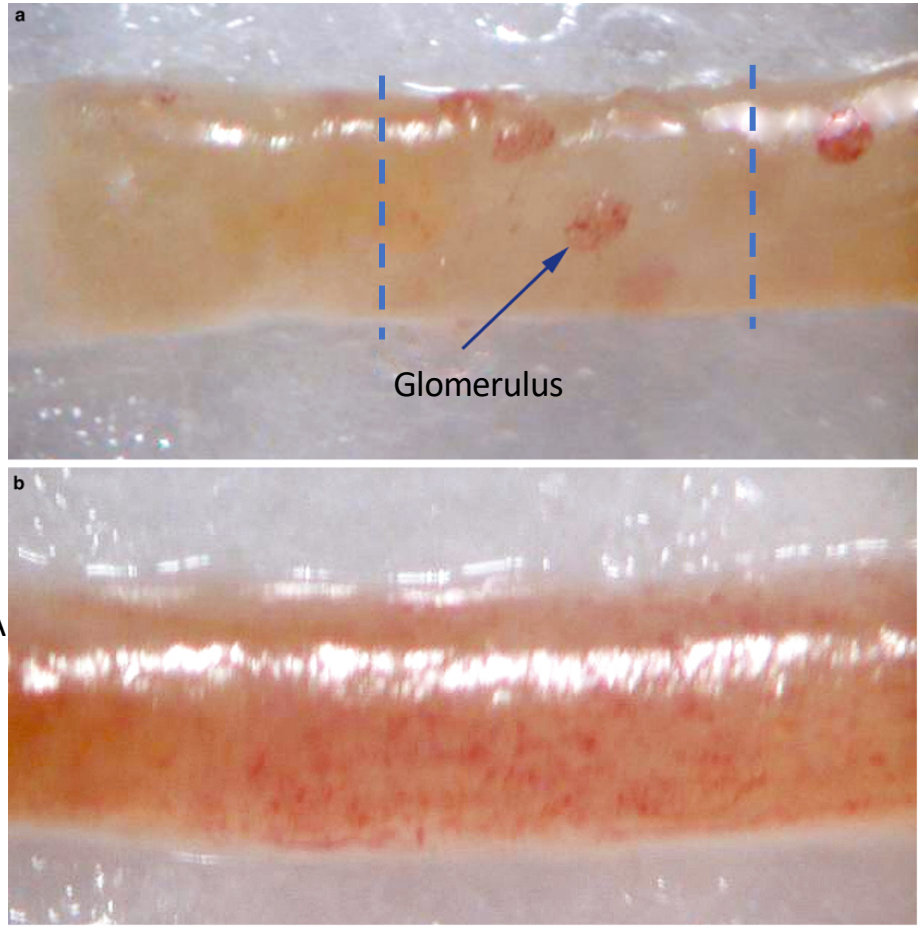


The renal biopsy is first examined under low-power magnification to determine the quality of the sample and search for focal lesions. Representative tissue is then allocated for LM, IF, and EM.

From: https://basicmedicalkey.com/kidney-needle-biopsy-evaluation-for-adequacy/

CORTEX

MEDULLA



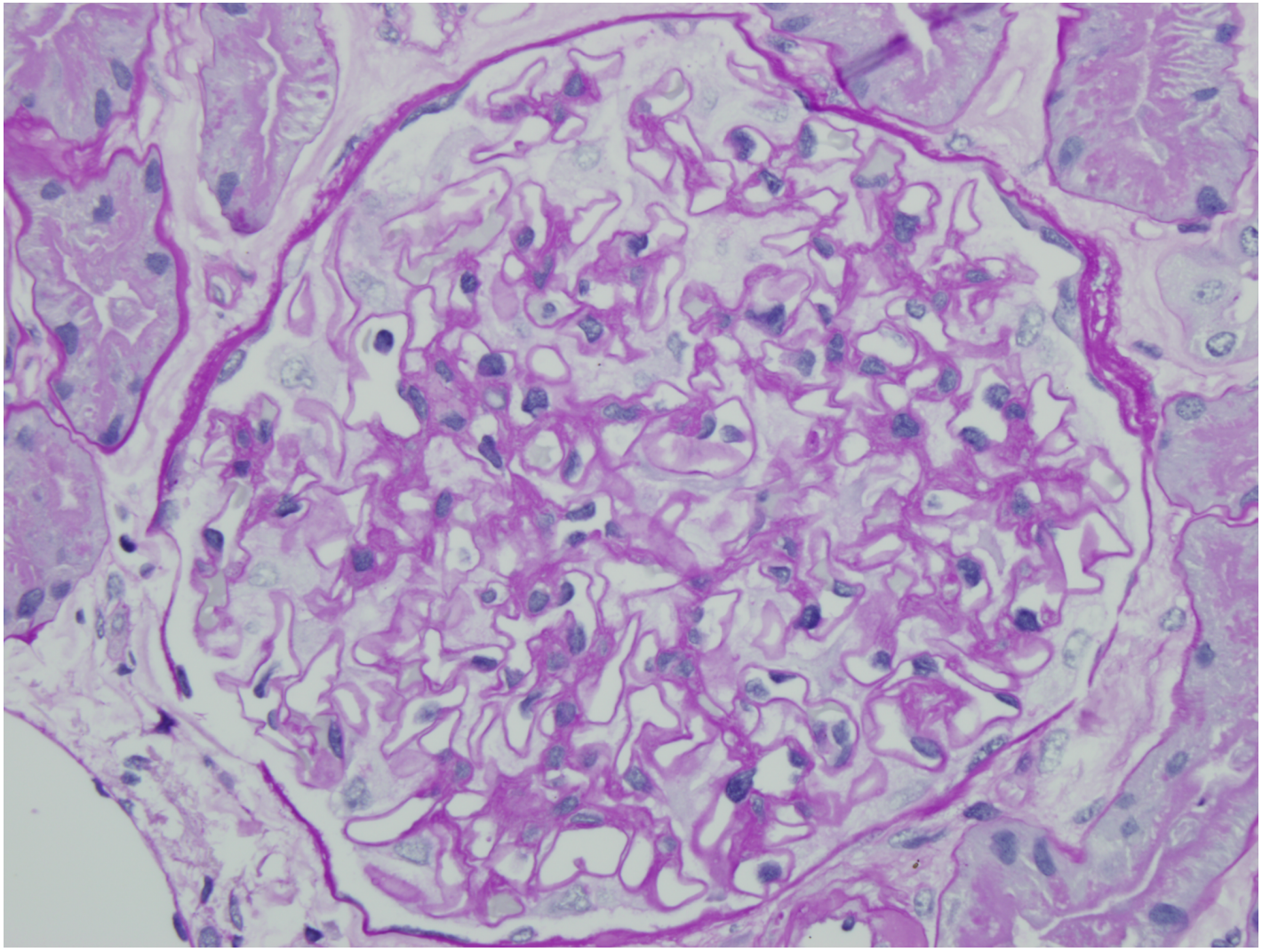
Kidney Pathology

- Light microscopy – uses different stains to evaluate different parts of the kidney. E.g. uses objectives to magnify eye vision up to 1000x.

- Electron microscopy – transmission beam, magnifies to 100,000x

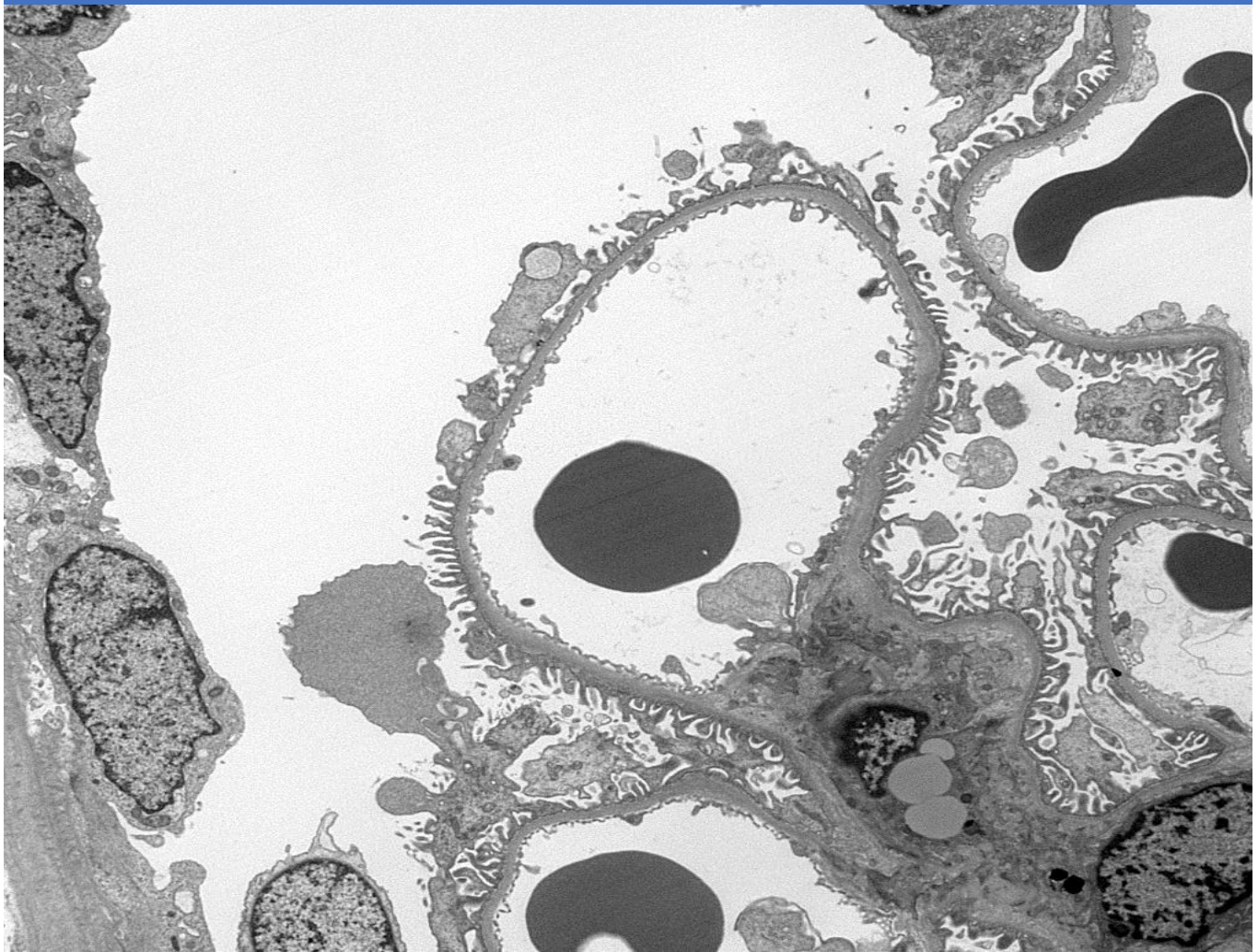
- Immunofluorescence microscopy – uses stains (antibodies) that fluoresce under the dark field microscope (same magnification as LM)

LM

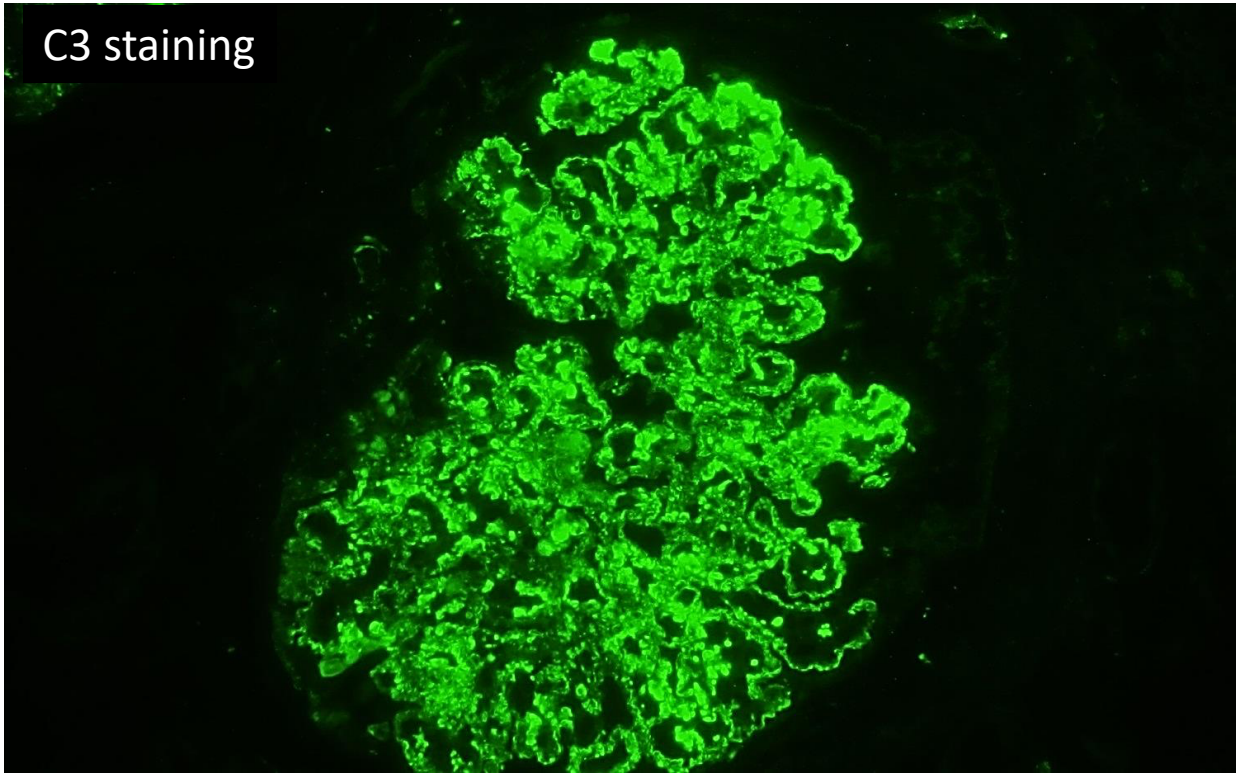


EM

Trent A., Bohlken, D. Department of Pathology. The University of Iowa Hospitals and Clinics Carver College of Medicine.



IF



Immunoglobulins (Ig): IgA, IgG, IgM
Complement (C): **C3** and C1q
Light chains: Kappa and lambda

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- **Blood tests; simple complement tests; urine tests**
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Smith et al *Nature Reviews Nephrol* 2019

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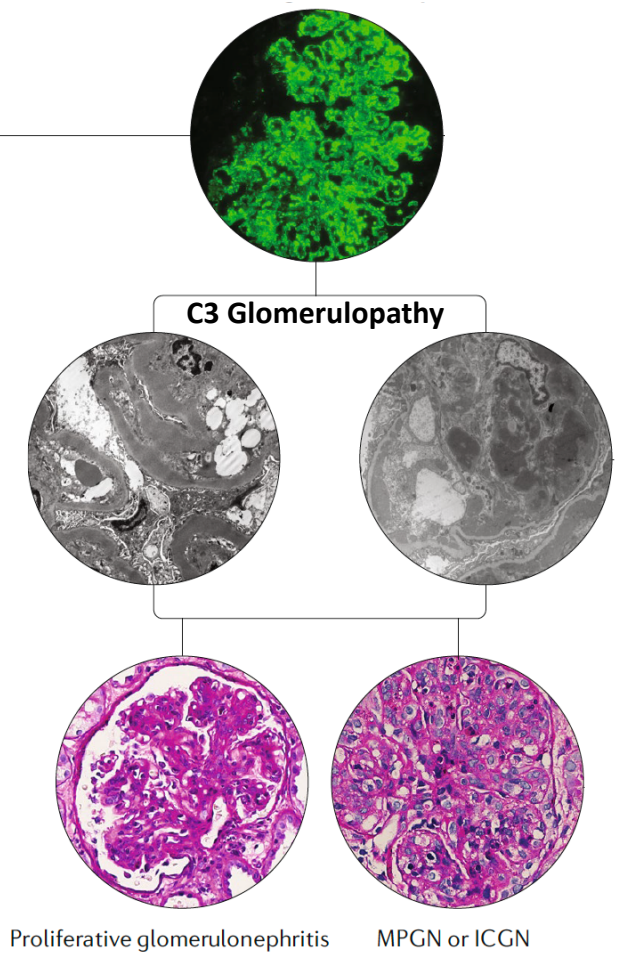

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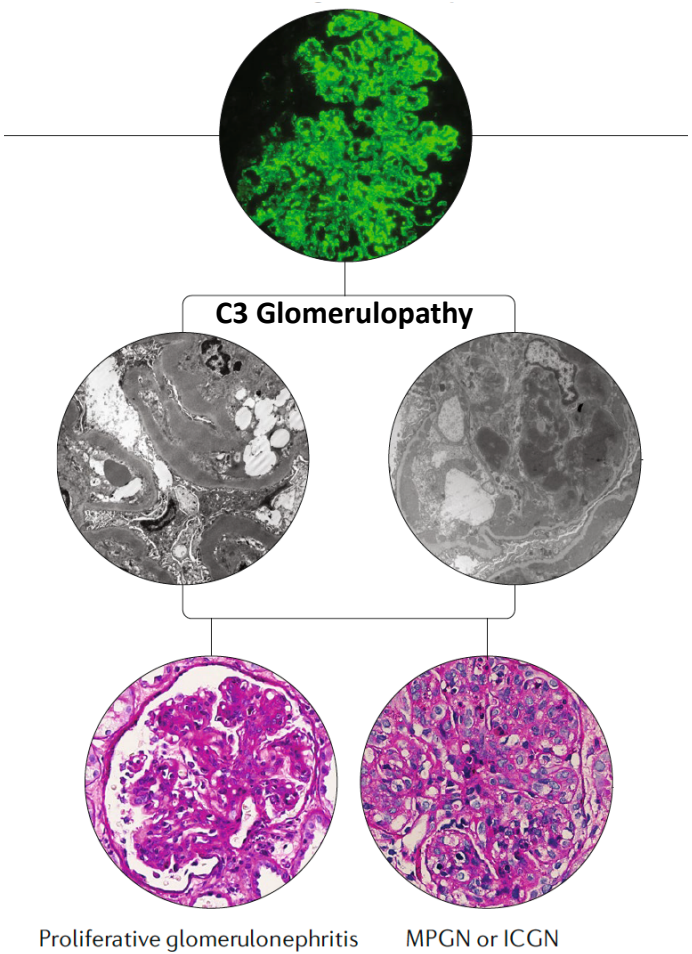
C3 Dominant Glomerulonephritis

Post-infectious GN

- 30% of cases are C3 dominant
- Complement abnormalities resolve within 8-12 weeks
- Persistent abnormalities = reclassification to C3G



Paraprotein-associated GN or MGRS

- Adults > 50 y/o
- Complement dysregulation driven by paraprotein
- Paraprotein-targeted therapy

Smith et al *Nature Reviews Nephrol* 2019

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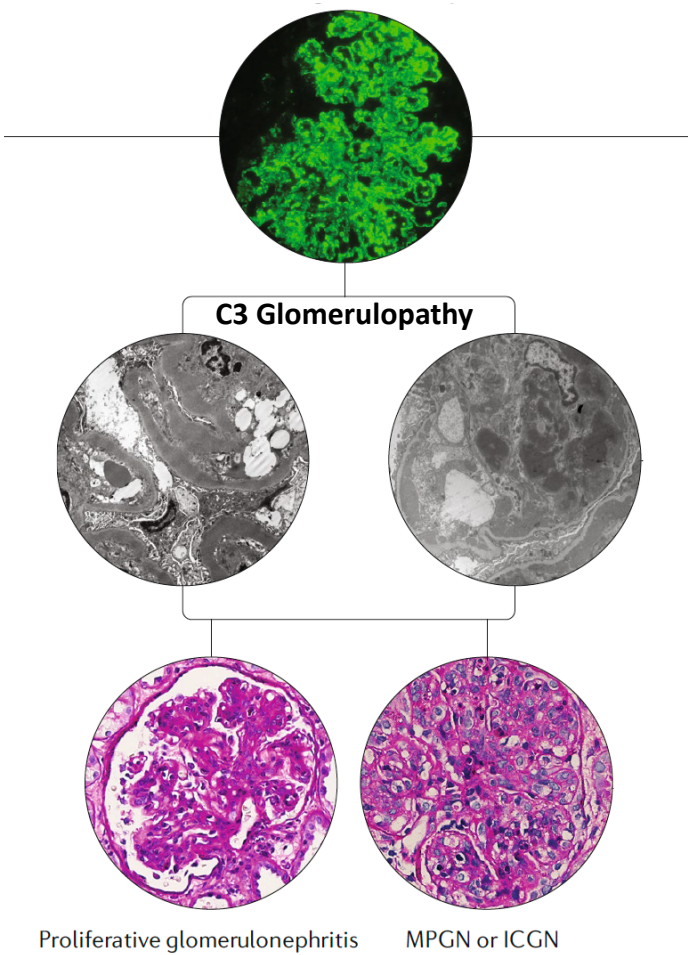

DDD
- **~20% of cases**
- **EM + highly electron-dense deposits**
- **Mass spectrometry shows complement components in the deposits**

C3GN
- **~80% of cases**
- **EM + electron-dense deposits lighter**
- **Increased likelihood of C5 convertase dysregulation**
- **Mass spectrometry shows complement components in the deposits**

Smith et al *Nature Reviews Nephrol* 2019

C3 Dominant Glomerulonephritis

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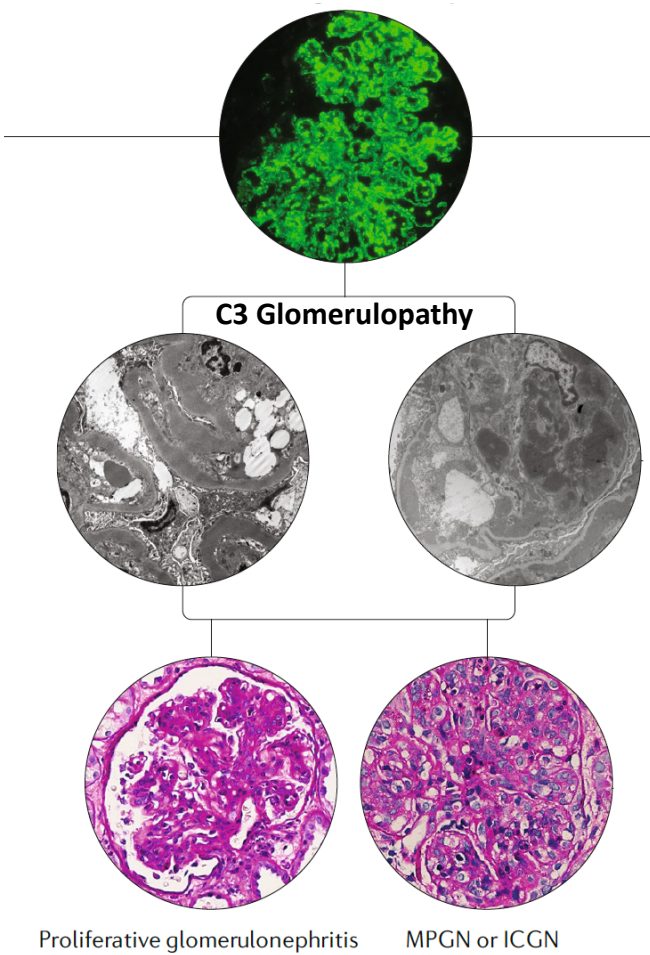

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- Mass spectrometry shows complement components in the deposits

C3GN
- ~80% of cases
- EM + electron-dense deposits lighter
- Increased likelihood of C5 convertase dysregulation
- Mass spectrometry shows complement components in the deposits

ICGN
- Can be associated with complement dysregulation
- ICGN can transition into C3G and vice versa

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- **Blood tests; simple complement tests; urine tests**
- **Biopsy *if* persistent proteinuria >500mg/24hrs *and/or* unexplained HTN with hematuria**

↓

Biopsy-confirmed C3 Dominant GN → **Exclude PIGN; MGRS if >50 y/o**

← **C3G**

↓

Measure complement levels and activity → **Recommended**
- **Complete complement biomarker profiling**
- **Nephritic factors assays**
- **Genetic testing (recommended before transplantation)**

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You are here → Patient Presentation

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- **Genetic testing (recommended before transplantation)**

↓

Treatment (based on disease activity)
- **Normal renal function and proteinuria <0.5g/24hr = supportive care**
- **Proteinuria 0.5g – 2.0g/24hr, moderate inflammation on bx, rise in SCr: MMF and prednisone (tapered)**
- **Proteinuria >2.0g/24hr, severe inflammation, progressive renal insufficiency: add pulse methylprednisolone**

Smith et al *Nature Reviews Nephrol* 2019

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Patient Presentation

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C3G

Measure complement levels and activity

Recommended

- **Complete complement biomarker profiling**
- **Nephritic factors assays**
- **Genetic testing (recommended before transplantation)**

Treatment (use anti-complement therapy)

- **Normal renal function and proteinuria <0.5g/24hr = supportive care**
- **Proteinuria 0.5g – 2.0g/24hr, moderate inflammation on bx, rise in SCr: MMF and prednisone (tapered)**
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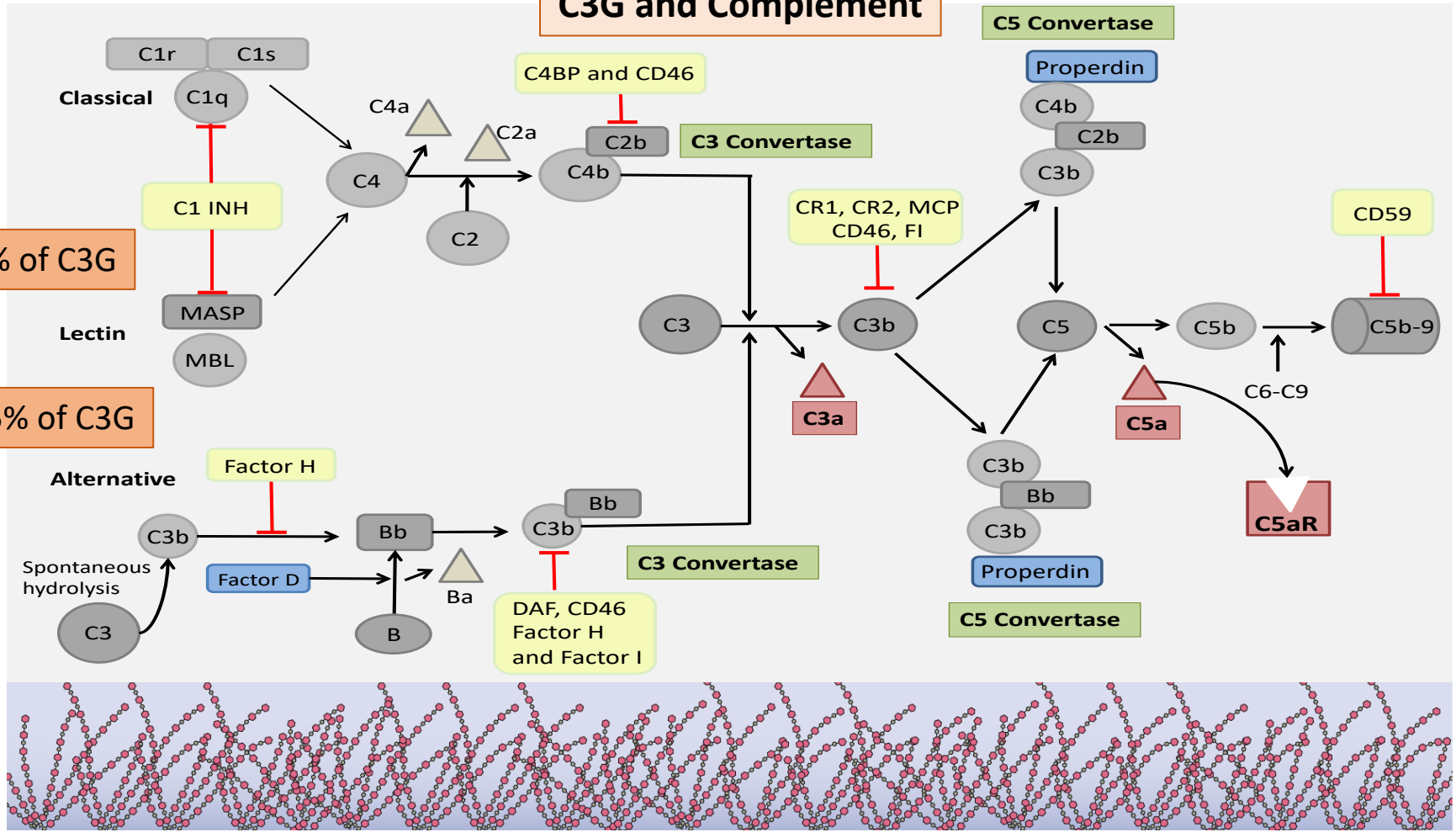
C3G and Complement



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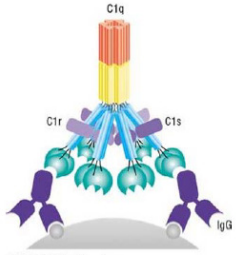
Phase 1: Initiation

Classical

Immune complexes

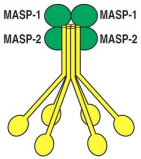


C4b 2a

C3 Convertase

Lectin

Microbial carbohydrates



Alternative

Activating surfaces

C3 B C3a Ba C3b Bb

C3 Convertase

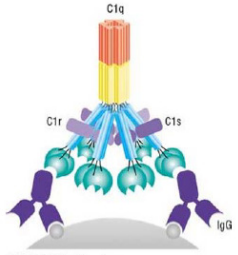
There are **three different ways** that complement can be initiated

- Classical pathway – detects antibodies to organisms
- Lectin pathway – detects sugars on bacteria
- Alternative pathway – always active at a low level
  - Process is called **tick-over**

Phase 1: Initiation

Classical

Immune complexes



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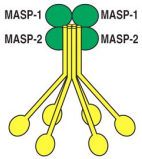


C3b Bb

C3 Convertase

C3 C3b

Alternative

Activating surfaces

C3 B

C3a Ba

C3b Bb

C3 Convertase

Phase 2: Amplification

Amplification is **driven** by C3 convertase

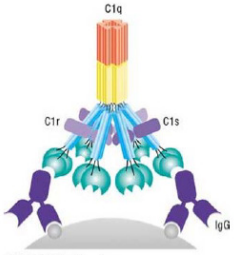
- C3 convertase converts C3 to C3a and C3b
- C3b is used to make more C3 convertase

Phase 1: Initiation

Phase 3: Effector

Classical

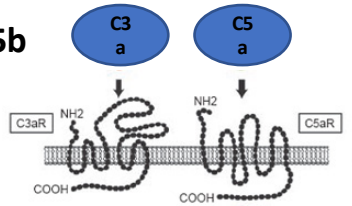
Immune complexes



The Effector Phase is the **Terminal Complement Cascade**

- TCC is triggered by the formation of **C5 convertase**
  - **Converts C5 into two pieces called C5a and C5b**
  - This sets the TCC in motion

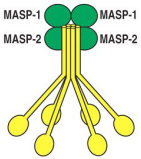
C3 Convertase

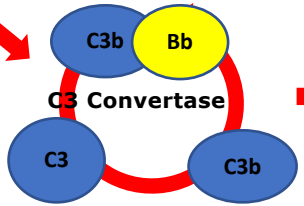


Inflammation

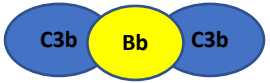
Lectin

Microbial carbohydrates

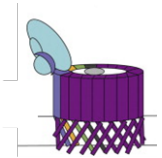




C3 Convertase

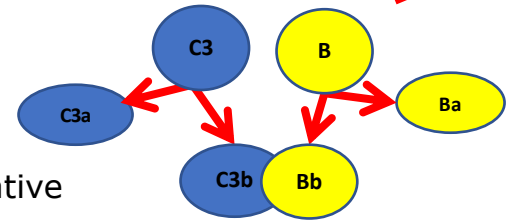


C5 Convertase



MAC

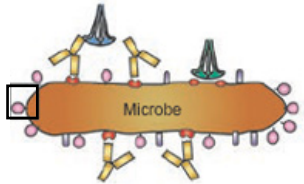
Activating surfaces



C3 Convertase

Phase 2: Amplification

Alternative



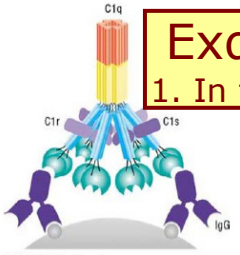
Opsonization

Phase 1: Initiation

Phase 3: Effector

Classical

Immune complexes



Exquisite control of complement is needed

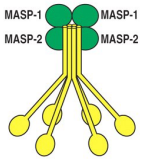
1. In the blood stream 2. On cell surfaces 3. In the glomerulus

C4b 2a

C3 Convertase

Lectin

Microbial carbohydrates



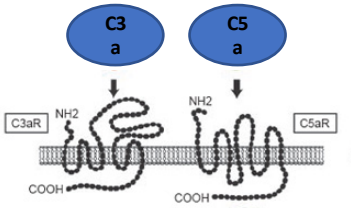
C3b Bb

C3 Convertase

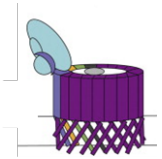
C3 C3b

C3b Bb C3b

C5 Convertase



Inflammation



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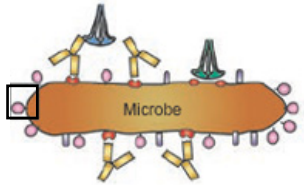
C3 Convertase

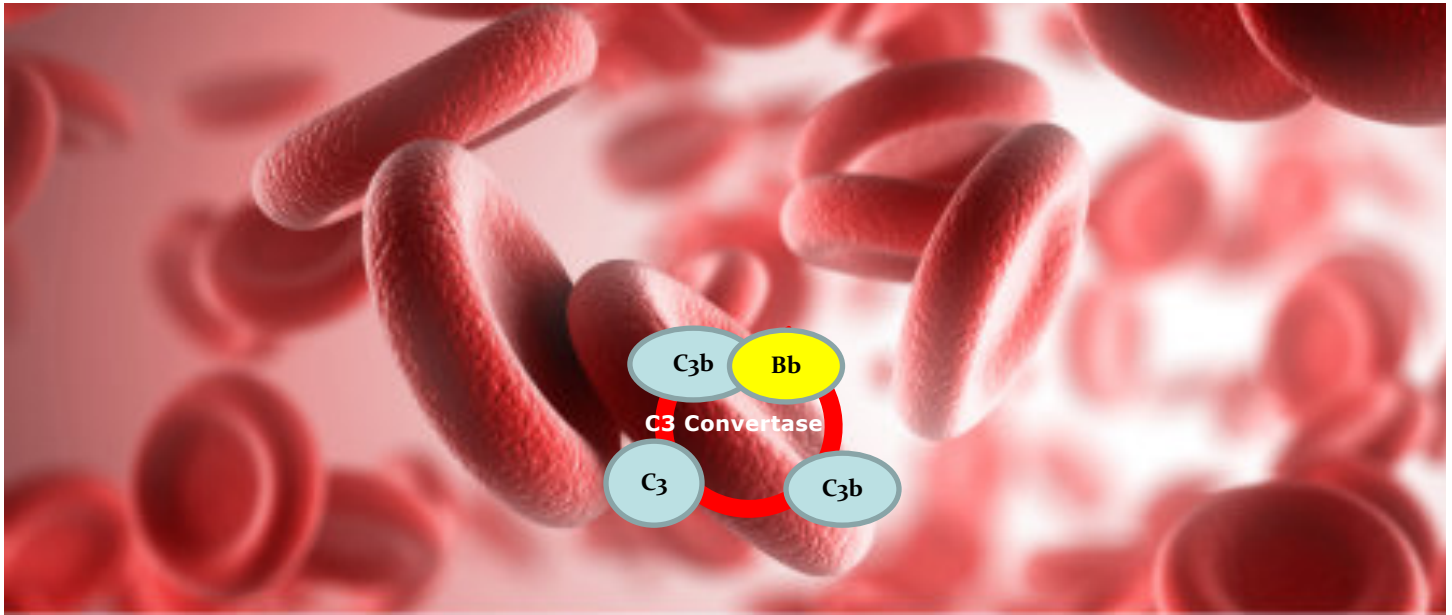
Phase 2: Amplification

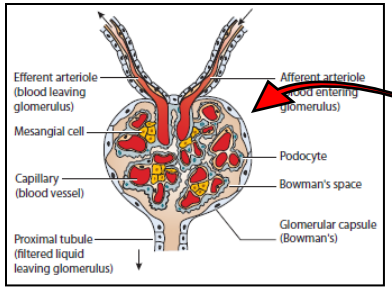
Alternative



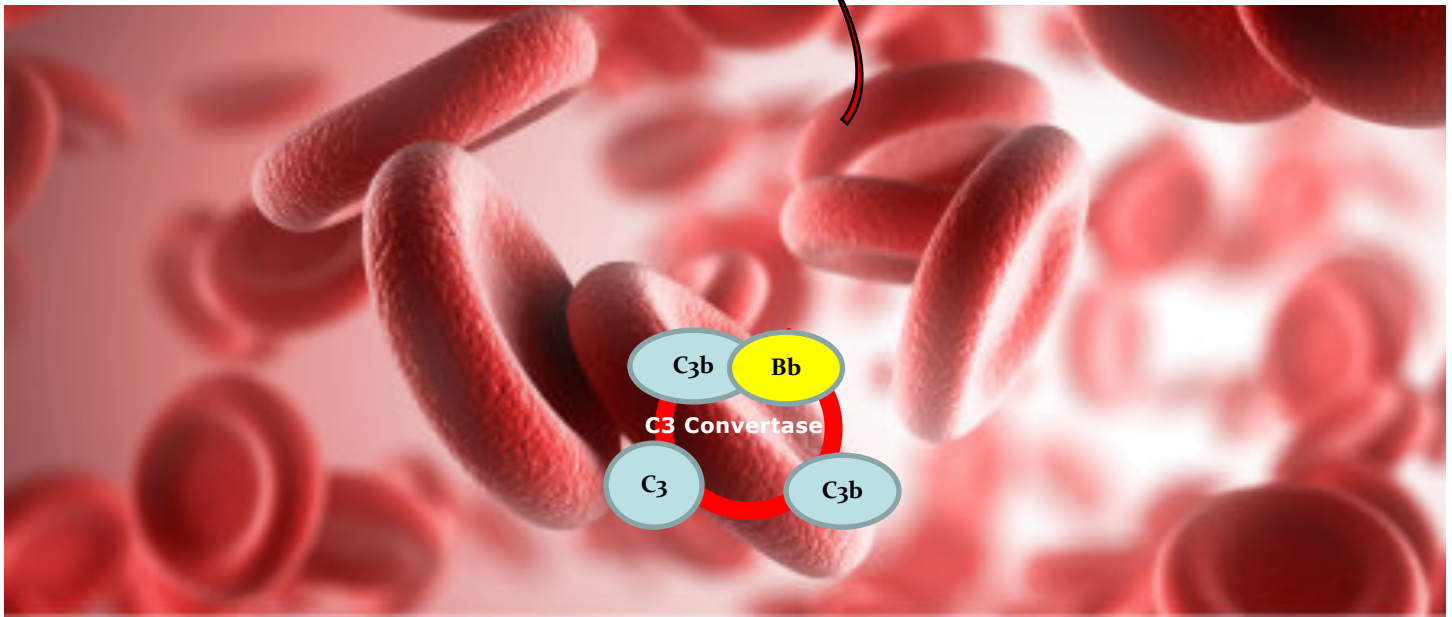
Opsonization

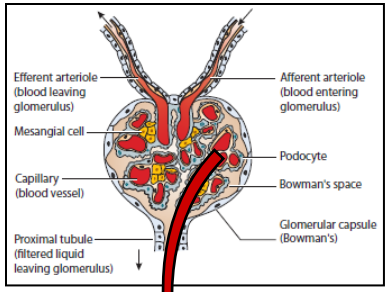
This a simplified view of tick-over occurring in the blood stream.





This a simplified view of tick-over occurring in the blood stream.
And in the renal glomerulus, where blood is concentrated and filtered.





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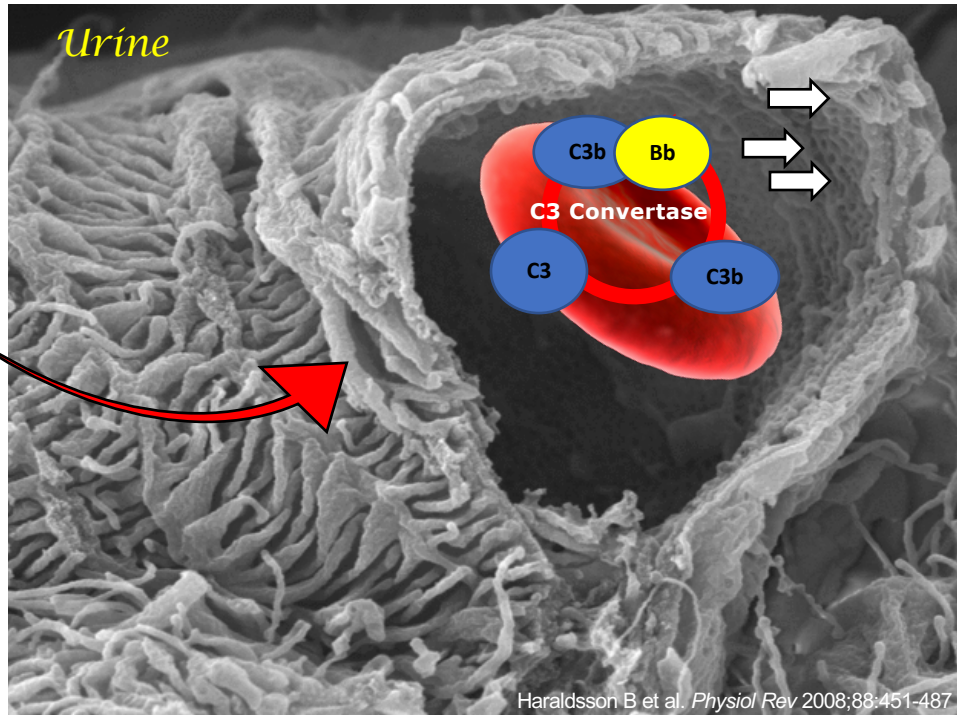
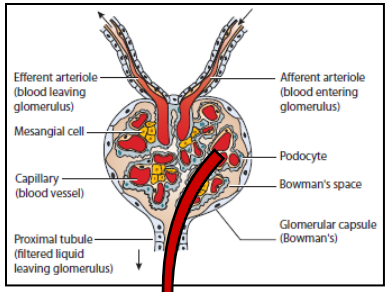
The glomerulus is unique because of the holes in the blood vessels.





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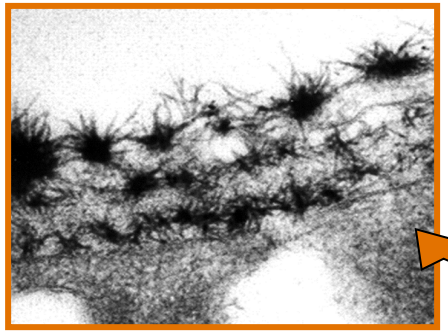
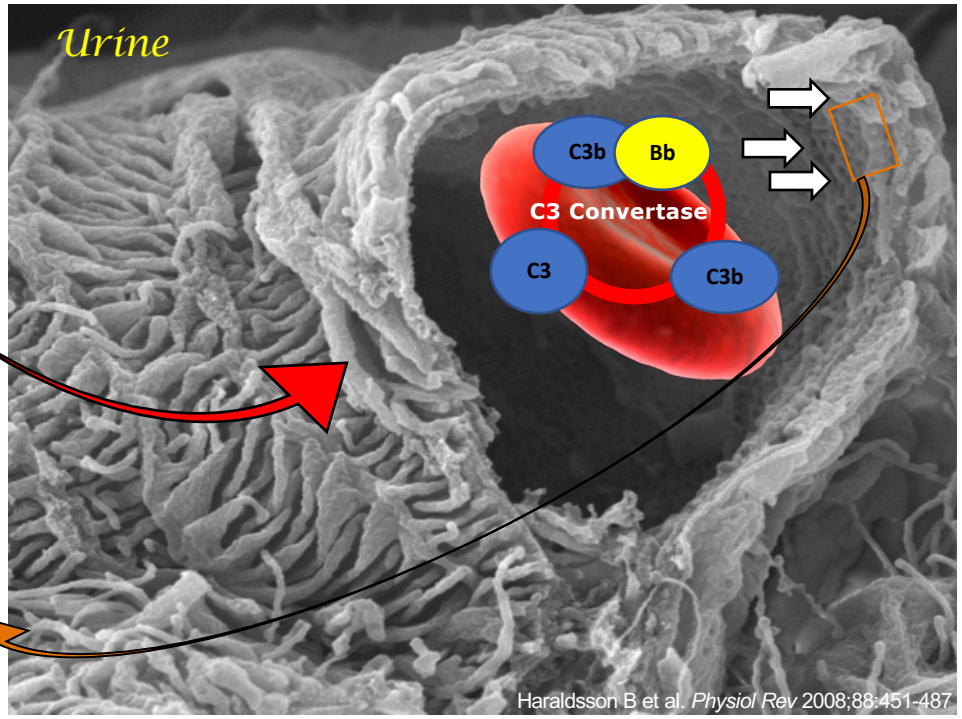


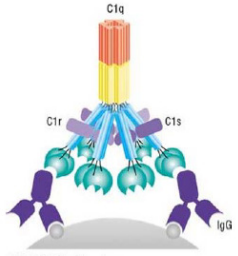


Phase 1: Initiation

Phase 3: Effector

Classical

Immune complexes

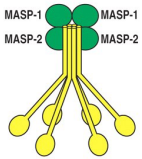


C4b 2a

C3 Convertase

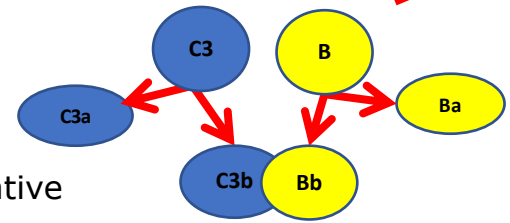
Lectin

Microbial carbohydrates



Alternative

Activating surfaces



C3 Convertase

Dysregulation

C3b Bb

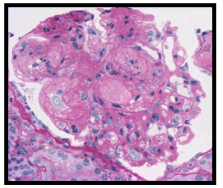
C3 Convertase

C3 C3b

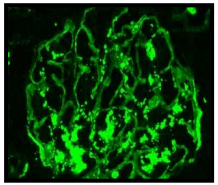
Phase 2: Amplification

C3b Bb C3b

C5 Convertase



aHUS
Cell surface

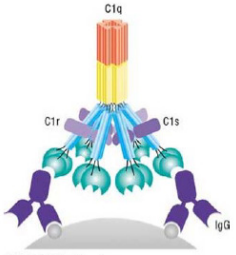


C3G
Blood stream

Phase 1: Initiation

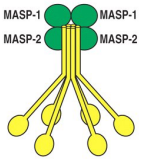
Classical

Immune complexes



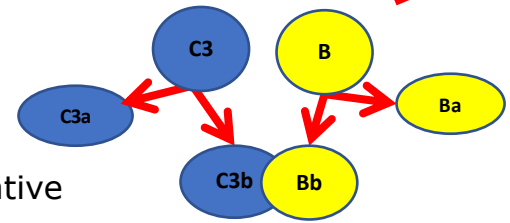
Lectin

Microbial carbohydrates

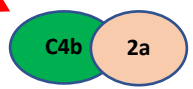


Alternative

Activating surfaces



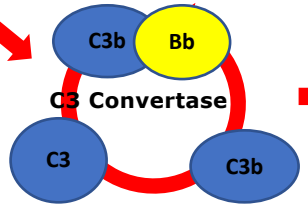
C3 Convertase



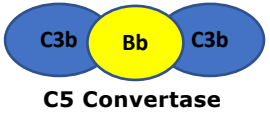
C3 Convertase

Phase 2: Amplification

Dysregulation occurs in the blood stream at the level of the C3 convertase and **lots** of C3 is consumed and lots of C3a and C3b are made



C3 Convertase

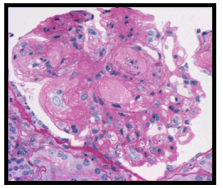


C5 Convertase

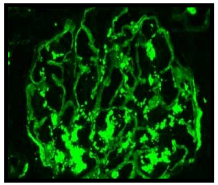
Phase 3: Effector

Dysregulation of C5 convertase can also occur and lots of C5a and soluble MAC are made

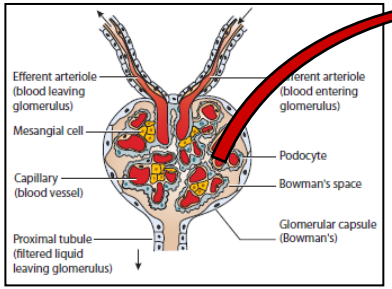
Dysregulation

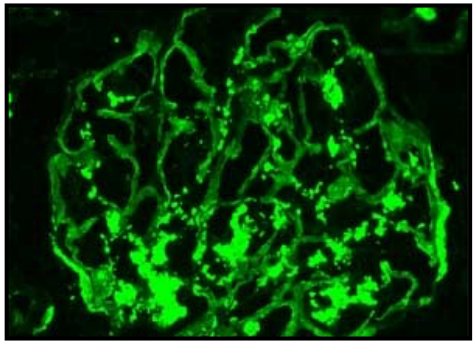


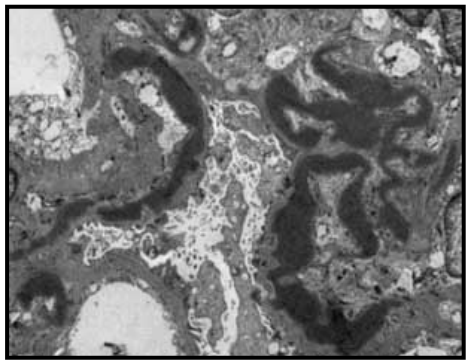
aHUS
Cell surface

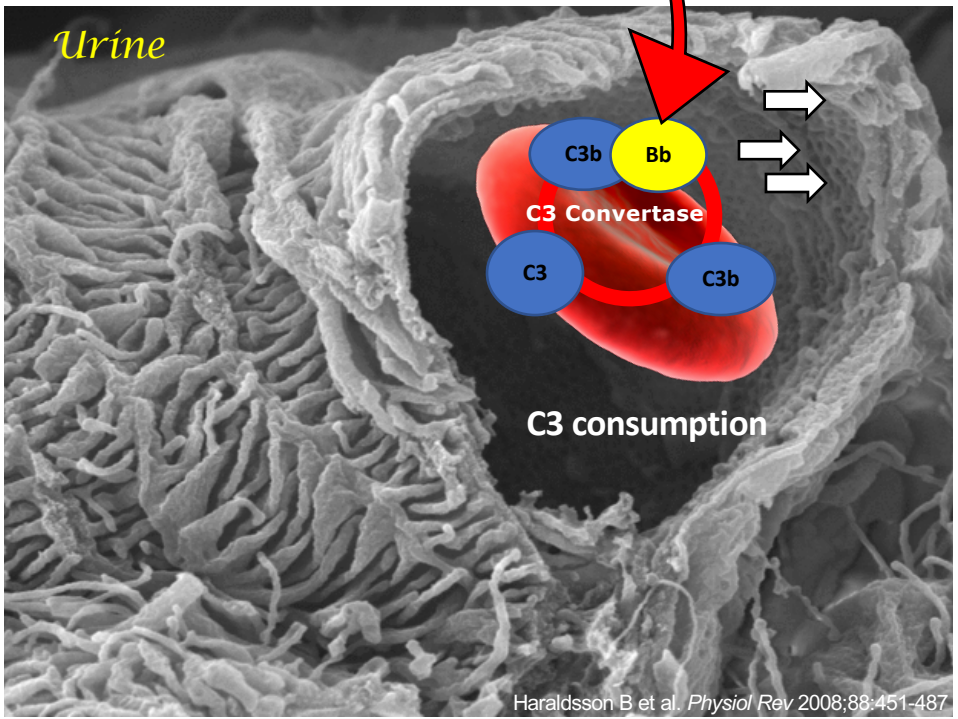


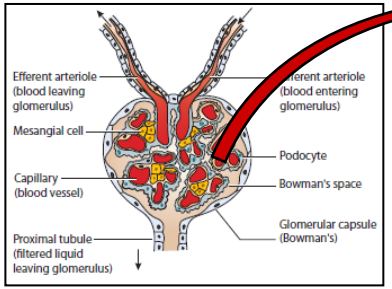
C3G
Blood stream


Efferent arteriole
(blood leaving
glomerulus)
Mesangial cell
Capillary
(blood vessel)
Proximal tubule
(filtered liquid
leaving glomerulus)
Afferent arteriole
(blood entering
glomerulus)
Podocyte
Bowman's space
Glomerular capsule
(Bowman's)

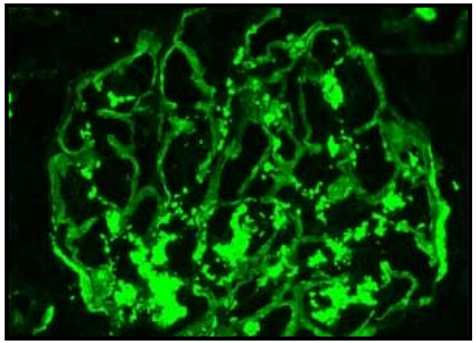


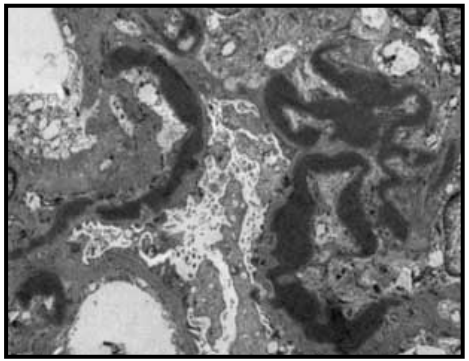


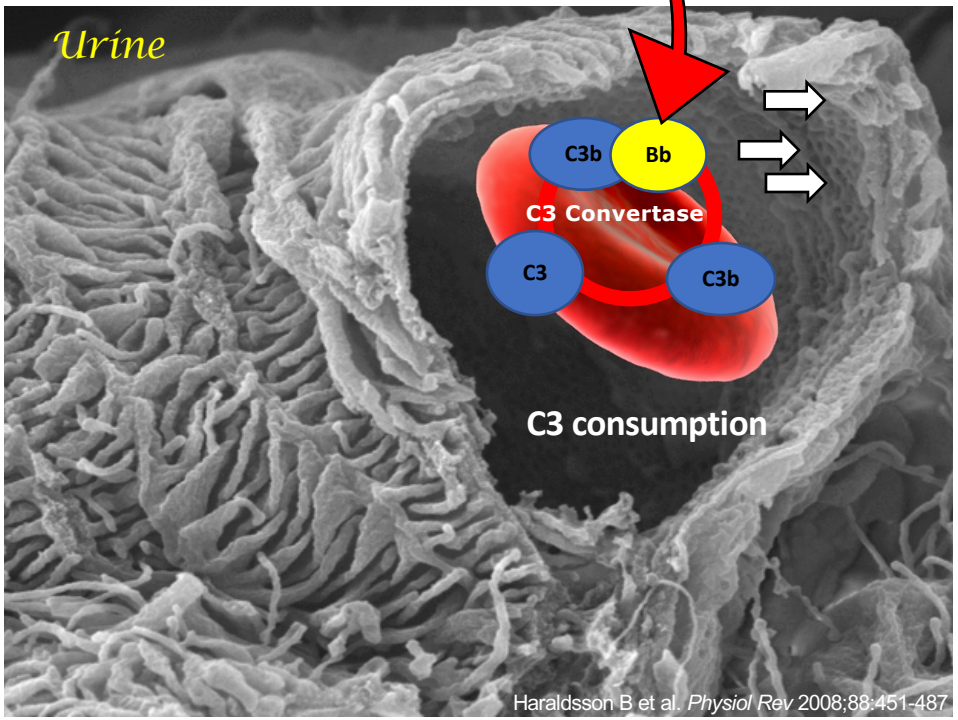

Urine
C3b
Bb
C3 Convertase
C3
C3b
C3 consumption
Haraldsson B et al. *Physiol Rev* 2008;88:451-487



In the blood stream, we can measure the complement proteins and infer what is happening in the circulation but we have to guess what is happening in the renal glomerulus



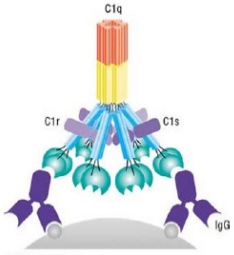




Phase 1: Initiation

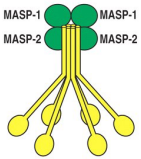
Classical

Immune complexes



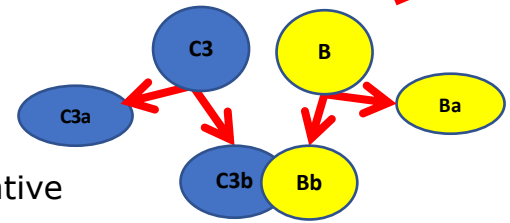
Lectin

Microbial carbohydrates



Alternative

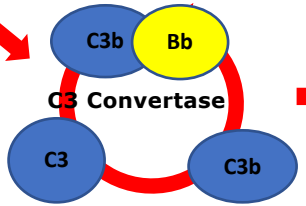
Activating surfaces

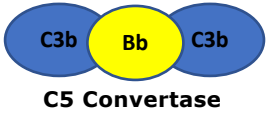


What Causes Dysregulation?

Phase 2: Amplification

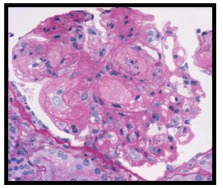
Dysregulation occurs in the blood stream at the level of the C3 convertase and **lots** of C3 is consumed and lots of C3a and C3b are made



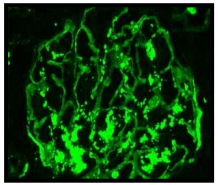


Phase 3: Effector

Dysregulation of C5 convertase can also occur and lots of C5a and soluble MAC are made

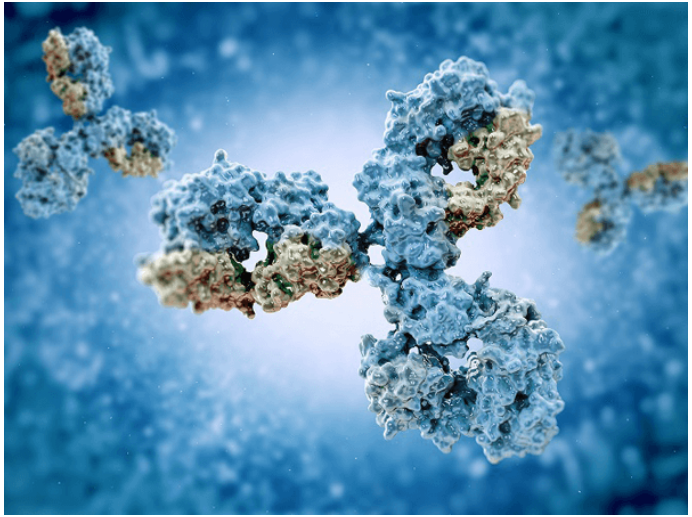


aHUS
Cell surface

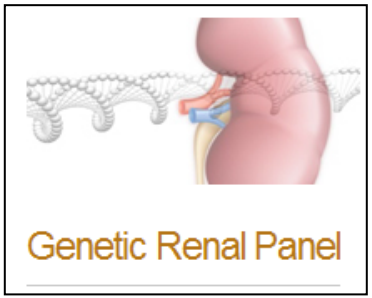


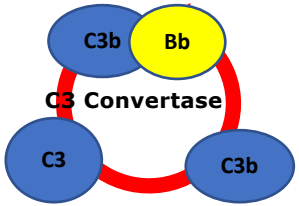
C3G
Blood stream

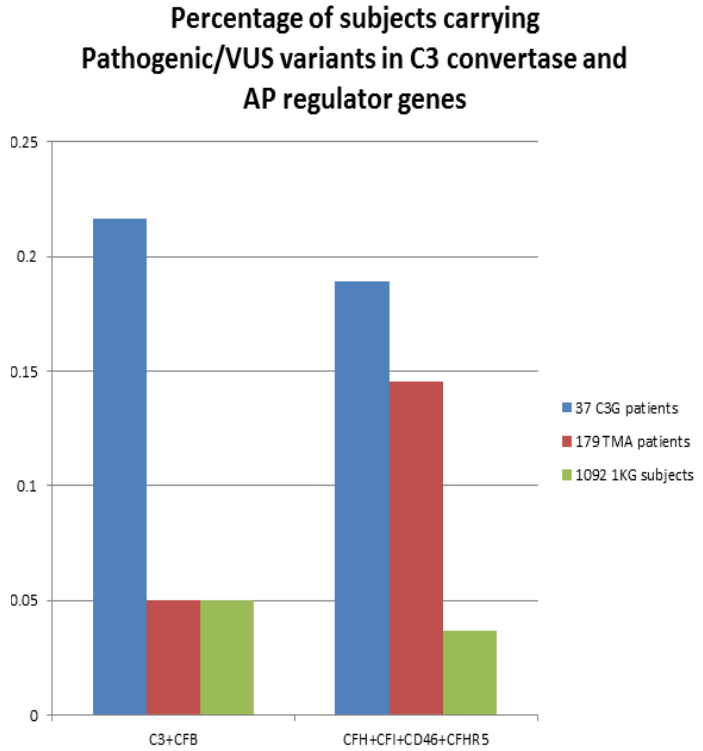
Genetics



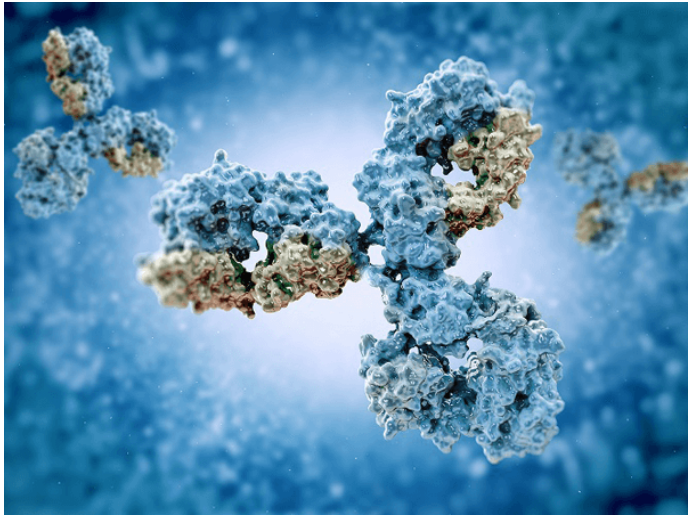
Autoantibodies







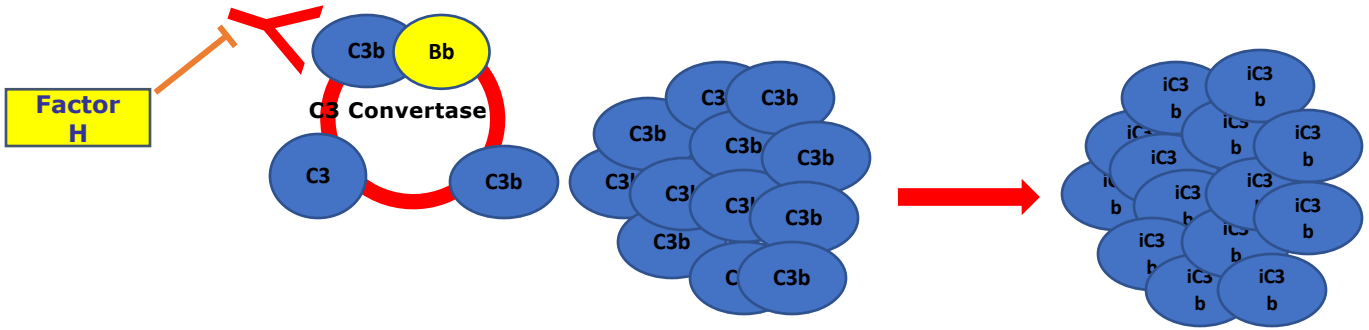
- About 20% of C3G patients carry rare genetic variants in *C3+CFB*
- These mutations stabilize C3 convertase

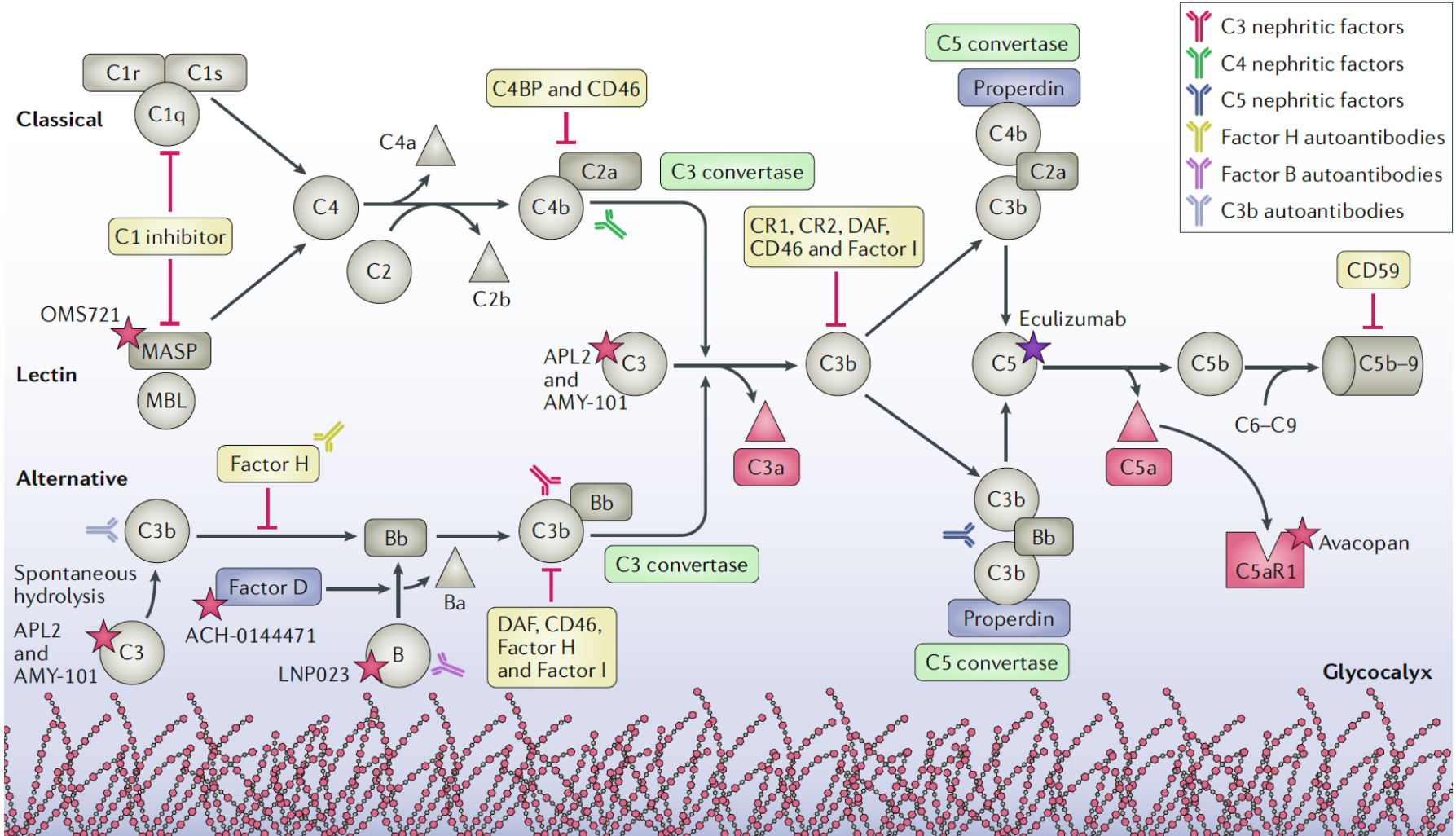


Autoantibodies

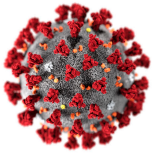
The most common acquired factors are autoantibodies to C3 convertase called **C3 nephritic factors (C3Nefs).**

- C3Nefs are present in about **80% of persons with DDD** and about **45% of persons with C3GN**.



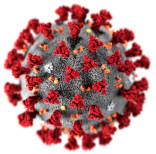

C3 nephritic factors
C4 nephritic factors
C5 nephritic factors
Factor H autoantibodies
Factor B autoantibodies
C3b autoantibodies
Classical
C1r
C1s
C1q
C1 inhibitor
C4
C4a
C2
C2b
C4BP and CD46
C2a
C4b
C3 convertase
C5 convertase
Properdin
C4b
C2a
C3b
CR1, CR2, DAF, CD46 and Factor I
CD59
Eculizumab
OMS721
MASP
Lectin
MBL
APL2 and AMY-101
C3
C3b
C5
C5b
C5b–9
C6–C9
C3a
C5a
Alternative
Factor H
C3b
Bb
C3b
Bb
C3 convertase
Spontaneous hydrolysis
Factor D
Ba
C3b
Bb
C3b
Properdin
C5 convertase
Avacopan
C5aR1
APL2 and AMY-101
C3
ACH-0144471
B
LNP023
DAF, CD46, Factor H and Factor I
Glycocalyx

COVID and C3G



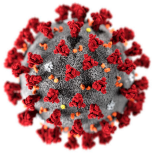
- COVID overview
  - ~80% have mild disease and recover spontaneously
  - ~20% present with severe disease
  - ~6% become critically ill
  - In symptomatic patients
    - Main signs include upper respiratory tract infection, cough, fever, loss of taste/smell, and weakness/lack of energy
    - Signs of severe disease include pneumonia with decreased oxygen saturation, lymphopenia and increased inflammatory markers (CRP, D-dimer, ferritin)

COVID and C3G



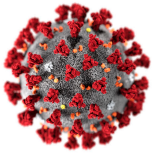
- Major risk factor for mortality
  - Advanced age
  - Of comorbidities like chronic kidney disease, hypertension, chronic obstructive pulmonary disease, diabetes, tumor and obesity, *advanced age the strongest predictor of a poor outcome*
- No study to date has found that chronic kidney disease is statistically correlated with severe COVID-19

COVID and C3G



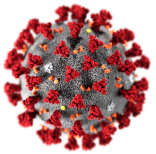
- The C3G patient
  - With their native kidneys
    - Has an underlying level of complement dysregulation
      - No data to suggest that makes COVID worse
      - Some animal data suggest the contrary (mice without C3 do better – Gralinski et al mBio, 2020)
    - Impact of COVID-19 on patients with *pre-existing* kidney impairment, including those with chronic kidney disease, not yet clearly established
    - Rules to *prevent* viral infection in the general population apply - hand hygiene, sanitization, social distancing, and avoiding areas where infected patients could be present

COVID and C3G



- The C3G patient
  - Who has a transplant
    - Is immunosuppressed
    - May have a higher risk of complications but published literature is skewed towards more serious cases (since patients without symptoms or minimal symptoms are rarely tested)
    - UIHC has treated about 10, most not admitted; 1 who needed ICU care
    - Rules to *prevent* viral infection in the general population apply - hand hygiene, sanitization, social distancing, and avoiding areas where infected patients could be present

COVID and C3G

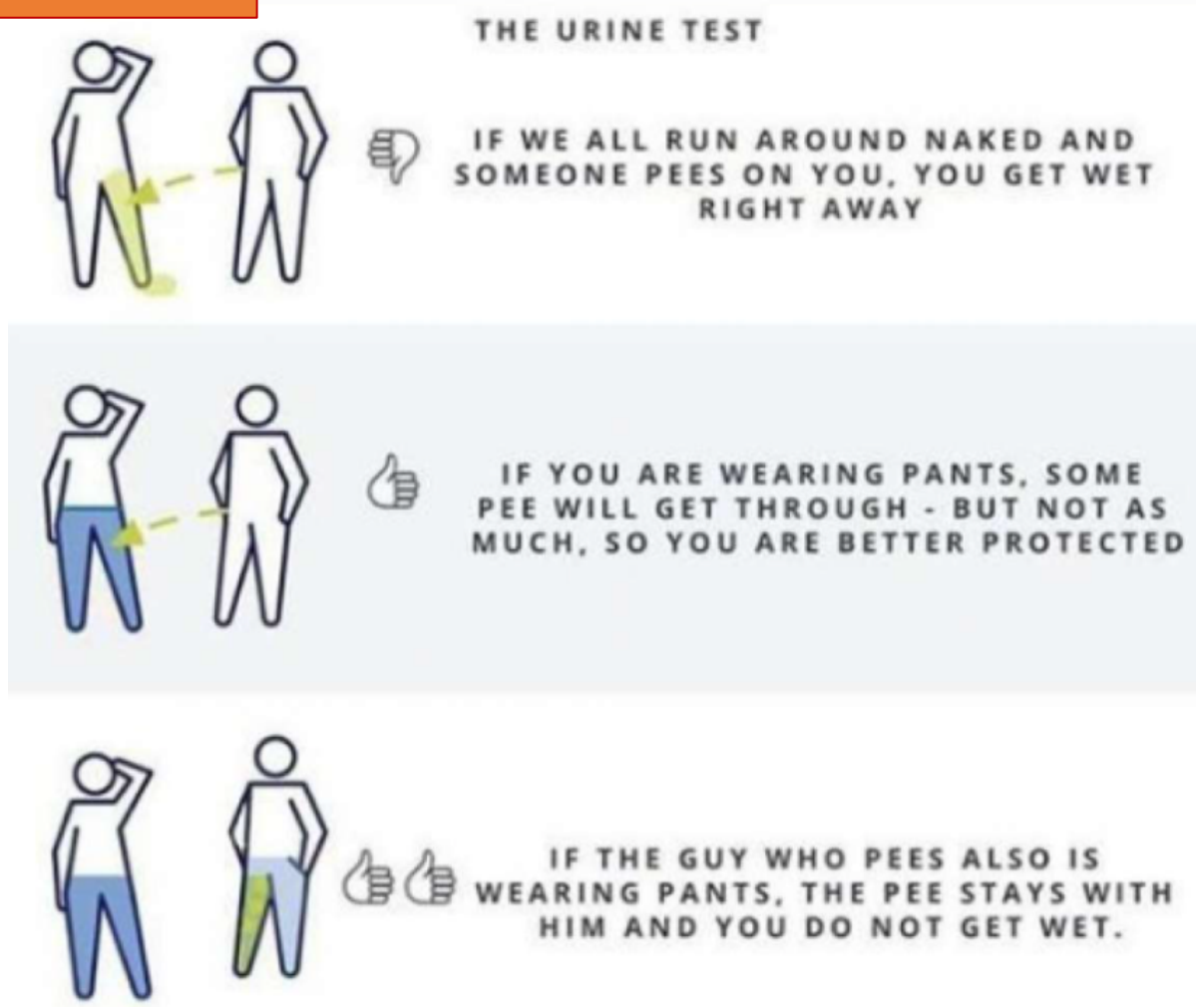


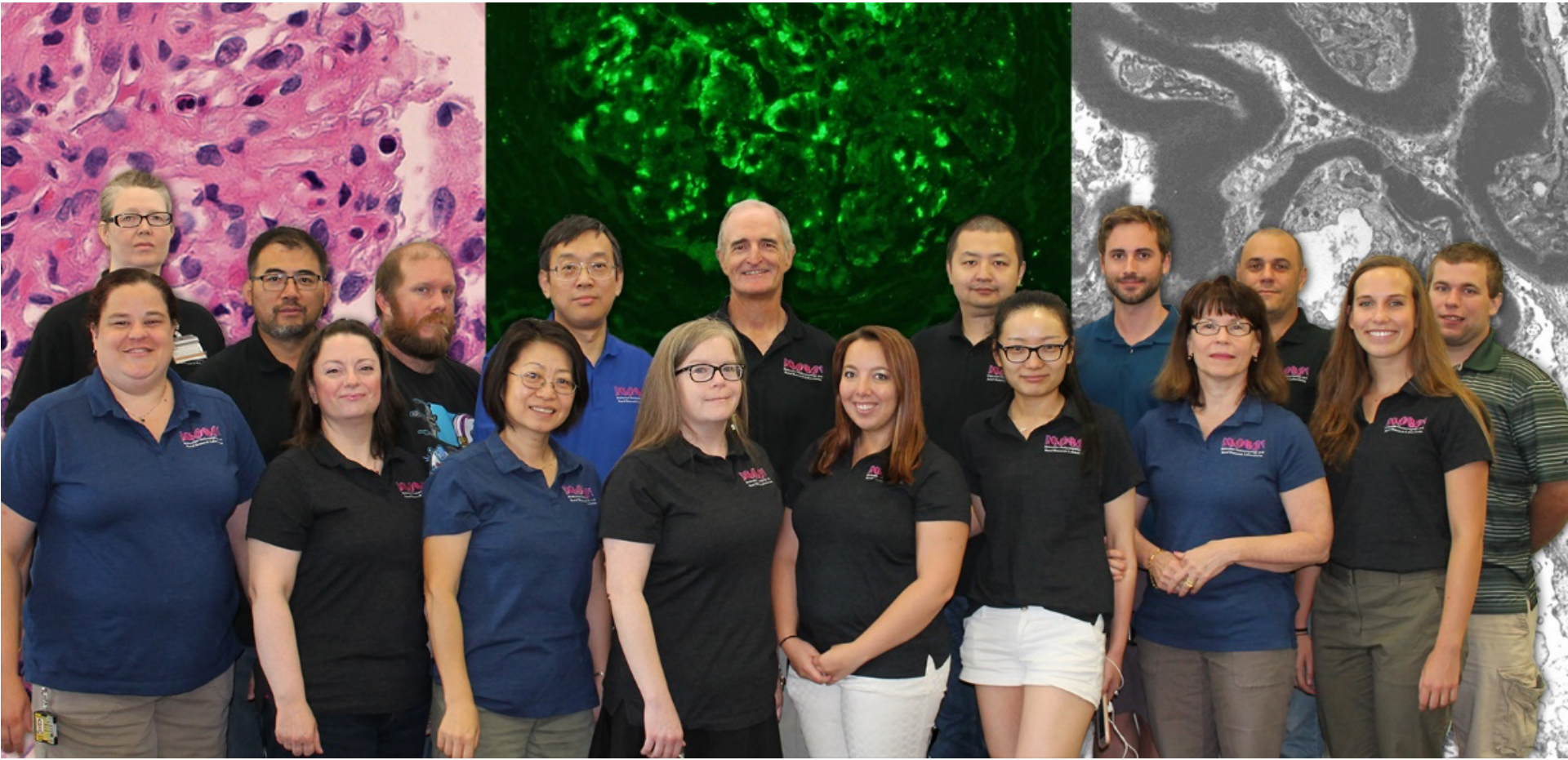
- The C3G patient
  - Already on anti-complement therapy
    - On-going anti-complement therapy with eculizumab or ravulizumab *may be* associated with more mild disease
      - Limited data but 8 patients with PNH and 1 patient s/p transplant for lupus nephritis with TMA
      - 8 patients had mild disease
      - 1 patient died: 43y/o BM with T2D, symptomatic for 10 days prior to seeking medical care (Araten et al JCaseRep, 2020; Kulasekararaj et al BJH, 2020; Pike et al, BJH, 2020)
    - Clinical trials underway with AMY-101, APL-9, eculizumab, ravulizumab, zilucoplan, avdoralimab and C1 esterase inhibitors
      - Target patients – those with severe disease and respiratory failure
      - Overactivation of complement postulated to trigger detrimental response (Holter et al PNAS, 2020)

Goals – to understand…….

- What C3G is
- How the kidney works and that C3G affects the glomerulus
- That other diseases can look like C3G
- That C3G is caused by complement dysregulation
- What the complement system does
- How we study complement in individual patients
- The many causes of complement dysregulation
- That while there are no disease-specific treatment, the future is *very* bright and multiple new therapies are being tested in clinical trials
- To remember rules to *prevent* viral infection in the general population apply to C3G patients - hand hygiene, sanitization, social distancing, and avoiding areas where infected patients could be present

So please, WEAR YOUR MASK





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