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
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
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Biopsy-confirmed C3 Dominant GN
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
For C3G we are interested in the glomerulus.
Cross section showing biopsy needle entering kidney
About 1 mm x 20 mm

From: https://basicmedicalkey.com/kidney-needle-biopsy-evaluation-for-adequacy/
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)
Immunoglobulins (Ig): IgA, IgG, IgM
Complement (C): C3 and C1q
Light chains: Kappa and lambda
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C3 Dominant Glomerulonephritis

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Smith et al Nature Reviews Nephrol 2019
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

- C3 Dominant Glomerulonephritis
- C3 Glomerulopathy
- Proliferative glomerulonephritis
- MPGN or ICGN

Smith et al Nature Reviews Nephrol 2019
C3 Dominant Glomerulonephritis

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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

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C3 Dominant Glomerulonephritis

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

Smith et al. Nature Reviews Nephrol 2019
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• Biopsy if persistent proteinuria >500mg/24hrs and/or unexplained HTN with hematuria

Patient Presentation

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

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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
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- Recommended
  - Complete complement biomarker profiling
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Patient Presentation

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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Phase 1: Initiation

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

C3 Convertase

C3a
Ba
B
C3
C4b
2a

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

Lectin

Microbial carbohydrates

C3 Convertase

C3
C3b
Bb

Activating surfaces

Alternative

C3 Convertase

C3a
B
Ba
C3b
Bb
Phase 1: Initiation

Classical

- Immune complexes
- Microbial carbohydrates
- Activating surfaces

Lectin

Phase 2: Amplification

- C3 Convertase
- C3b Bb C3b
- C5 Convertase
- C3b Bb C3b

Phase 3: Effector

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

Opsonization

MAC

Inflammation

Opsonization
Phase 1: Initiation

Classical

Immune complexes

Microbial carbohydrates

Lectin

Activating surfaces

Alternative

Exquisite control of complement is needed
1. In the blood stream 2. On cell surfaces 3. In the glomerulus

Phase 2: Amplification

C3 Convertase

Phase 3: Effector

Inflammation

MAC

Opsonization

C3a

C5a

C3

C5 Convertase

Opsonization

C3b

Bb

C3b

Bb

C3 Convertase

C3b

Bb

C3 Convertase

C3b

Bb

C3b
This a simplified view of tick-over occurring in the blood stream.
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And in the renal glomerulus, where blood is concentrated and filtered.
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Immune complexes

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C4b

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B

Bb

C5 Convertase

Phase 2: Amplification

C3 Convertase

C3

C3b

Bb

C3b

Bb

C5 Convertase

Phase 3: Effector

Dysregulation

aHUS

Cell surface

C3G

Blood stream
Phase 1: Initiation

Classical

- Immune complexes
- Microbial carbohydrates
- Activating surfaces

Lectin

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

- Blood stream

- C3G
C3 Convertase

C3b

C3

C3b

Bb

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.
What Causes Dysregulation?

Phase 1: Initiation

Classical

- Immune complexes
- Microbial carbohydrates
- Activating surfaces

Lectin

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
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.
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; Kulasekaranaraj 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)
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- 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

THE URINE TEST

IF WE ALL RUN AROUND NAKED AND SOMEONE PEES ON YOU, YOU GET WET RIGHT AWAY

IF YOU ARE WEARING PANTS, SOME PEE WILL GET THROUGH - BUT NOT AS MUCH, SO YOU ARE BETTER PROTECTED

IF THE GUY WHO PEES ALSO IS WEARING PANTS, THE PEE STAYS WITH HIM AND YOU DO NOT GET WET.
Funding: NIH, Novartis and private philanthropy