University of Iowa
Stead Family
Children's Hospital

# C3 Glomerulopathy

## Current Cares

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C3 Glomerulopathy Family Support Group – October 2022

# Disclosures

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The following includes a list of current (within the last 24 months) affiliations:

| Affiliation / Financial Interest | Organization |
|---|---|
| Associate Director | Molecular Otolaryngology and Renal Research Laboratory |
| NIH | 1R01DK110023-01A1 |
| Site Investigator | ChemoCentryx |
| Site Investigator | Alexion Pharmaceuticals |
| Site Investigator, Advisory Board | Novartis |
| Site Investigator | Retrophin |
| Site Investigator, Advisory Board | BioCryst |
| Site Investigator, Advisory Board | Apellis |
| Data Safety Monitoring Board | Kira |
| Author Royalties | UpToDate |

My conflicts are managed by a University of Iowa mandatory conflict plan.
Both prior and current relationships are on record at the University of Iowa's Conflict in Research Office:
https://coi.research.uiowa.edu/

# Nomenclature

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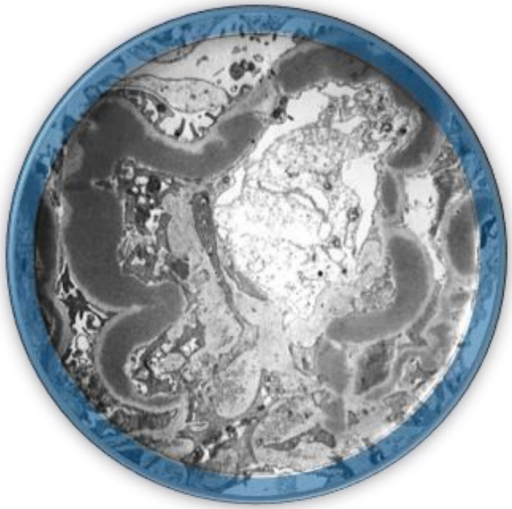
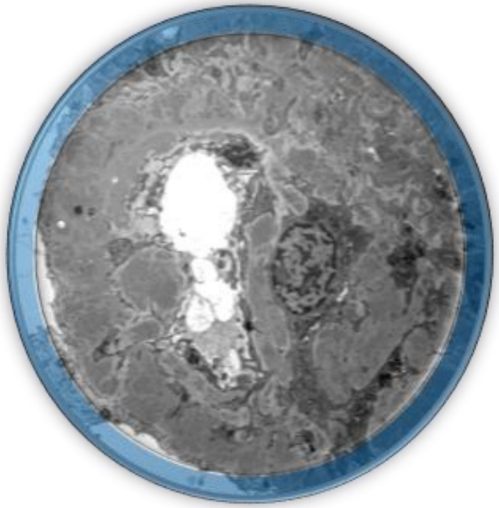
- *C3 Glomerulopathy*
  - Term used to designate a disease process
- *C3 Dominant Glomerulonephritis (Glomerulonephritis with dominant C3 )*
  - The pathologic description of C3G AND "*PIGN*"
- *C3 Glomerulonephritis*
  - One of two types of C3G
- Dense Deposit Disease





Kidney Int. 2013 Dec;84(6):1079-89

## Objectives

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- Recognize the initial approach to C3 Glomerulopathy
- Understand when mycophenolate mofetil (MMF) and steroids should be considered
- Brief review of pros and cons of steroids
- Understand indication for when care should be escalated

# How C3G Patients Present

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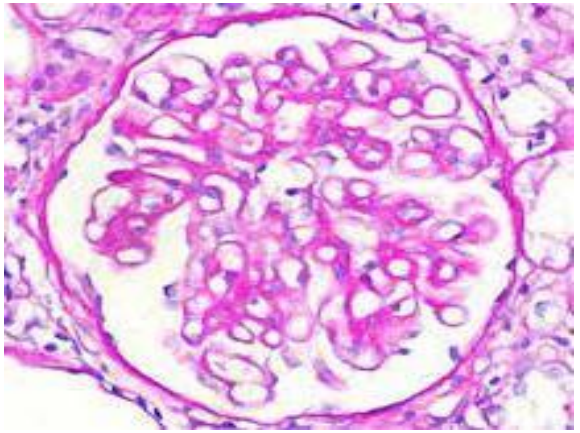
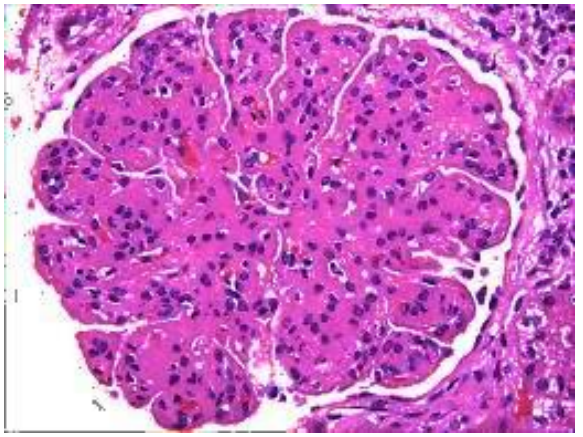
1. Clinical presentation of *glomerulonephritis* (hematuria, proteinuria, HTN, etc)
   a. Can be confused with other causes of hematuria, proteinuria or hypertension
2. Ruling out infection related disease is crucial:
   a. Renal biopsy that meets diagnostic criteria – and has been taken at least 12 weeks after purported infection.
      I. (C3G and PIGN biopsies are indistinguishable)
   b. Goal: rule out normal complement activation process





# Paraprotein Related C3 Glomerulopathy

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- Paraproteins are abnormal proteins made by a "rogue" cell in your body.
  - Usually occurs in someone older than 50
  - Can dysregulate the complement pathway (kind of like nephritic factor)
  - Monoclonal gammopathy of renal significance (MGRS)
  - Incidence varies:  33-83%
    - Am J Kidney Dis. 2010 Nov;56(5):977-82
    - Treating the paraprotein gives better renal survival
  - KDIGO guidelines support evaluating for the presence of a paraprotein in ALL patients who present with C3G for the first time over the age of 50.

Blood. 2017;129(11):1437-1447

# Controversies related to diagnosing C3G

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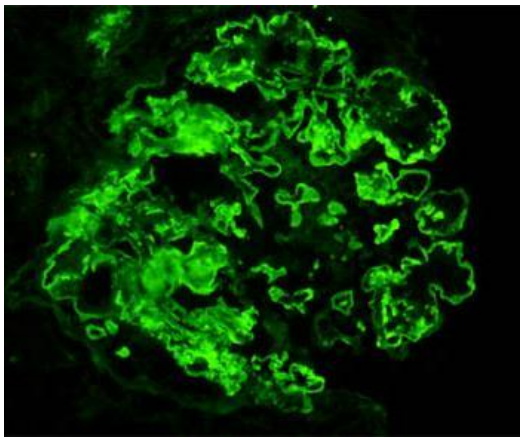
- Does not have to be "isolated" C3 deposits
  - Hou et al.: 41% of cases have C3 only, IgM is often "trapped" in this setting (59%)
- Light microscopy pattern is variable (absence of MPGN pattern is common).
- Ruling out infection related disease is crucial:
  - Renal biopsy that meets diagnostic criteria – and has been taken at least 12 weeks after purported infection.
    - (C3G and PIGN biopsies are indistinguishable)
  - Goal: rule out *normal* complement activation process
- The Biopsy may not be static: C3G →← MPGN (ICGN)
  - (8% of repeat biopsies went from ICGN to C3G)



Kidney Int. 2014 Feb;85(2):450-6

# Current Recommendations for Treatment

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**All patients should receive supportive cares**

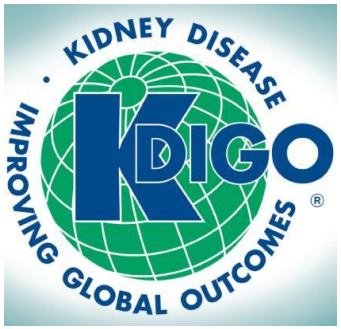
- **Optimal blood pressure control**
- **Optimal nutrition for both normal growth in children and healthy weight in adults**

**In the absence of a monoclonal gammopathy, consider treating patients with:**

- **>1g/d of urine protein**
- **Declining kidney function (over 6 months)**

**Initial treatment:**

- **Mycophenolate mofetil + steroids**
- **If above fails – consider eculizumab**
- **Consider for clinical trial**




Chapter 8

- Not based on trial data
- Retrospective
- Generic approach: a trial of things that were used in other glomerular diseases
  - Limited availability of "targeted" therapeutics

Kidney International (2021) 100, 753-779

# Renal Response to Current Cares

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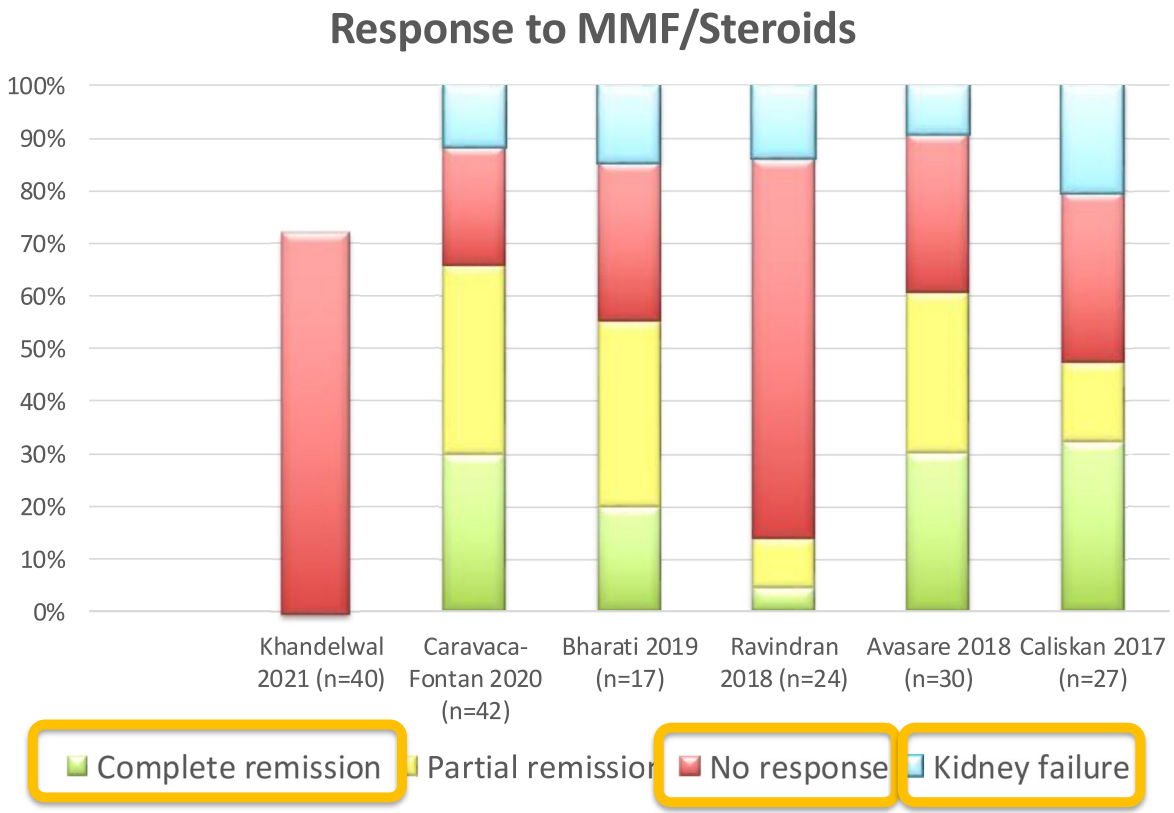


- Current cares are guideline based
- Doses and duration vary
  - No guideline for dose and duration of steroids
- Follow-up is variable
- Criteria for response is variable

- Response highly variable across studies

# Eculizumab and C3G

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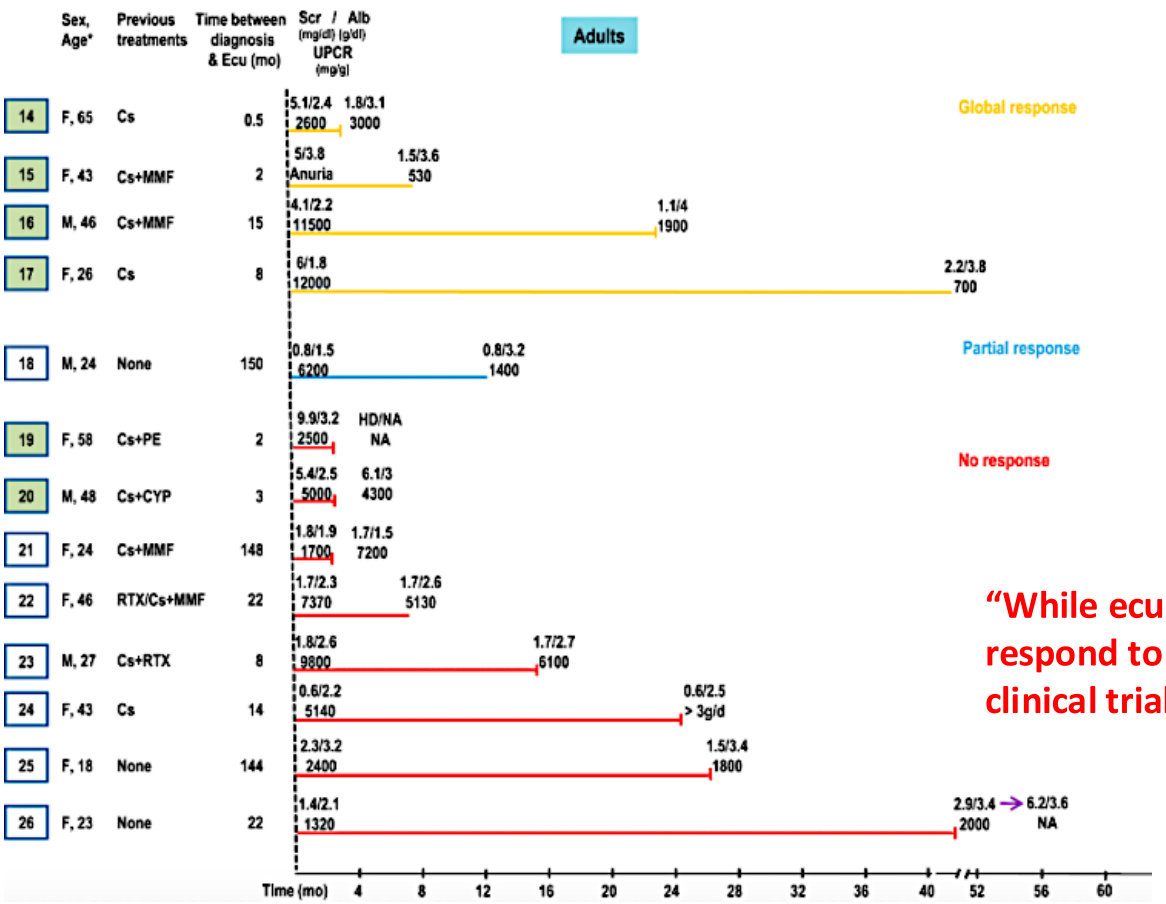


- 6/26 complete remission
- 1/26 partial remission
  - Response was not predicted by sMAC (C5b-9)

**"While eculizumab can be tried in patients who fail to respond to MMF, such patients should be considered for clinical trials where available"**

No reason to think that the response to Ravulizumab would be different

Am J Kidney Dis. 2018 Jul;72(1):84-92

# Treatment Effect – Allograft Loss

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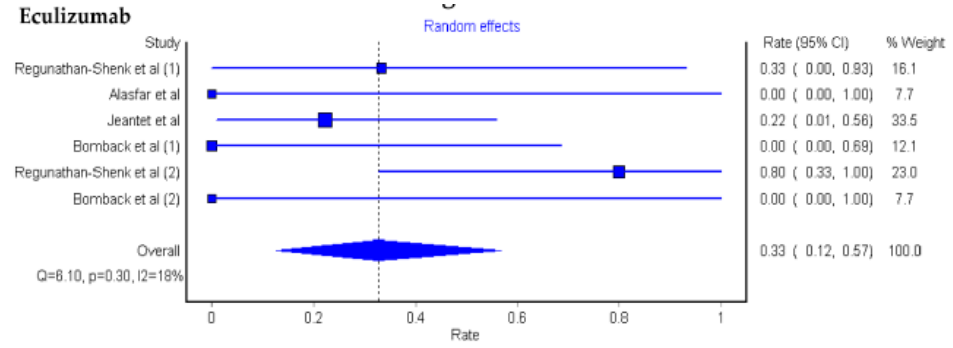


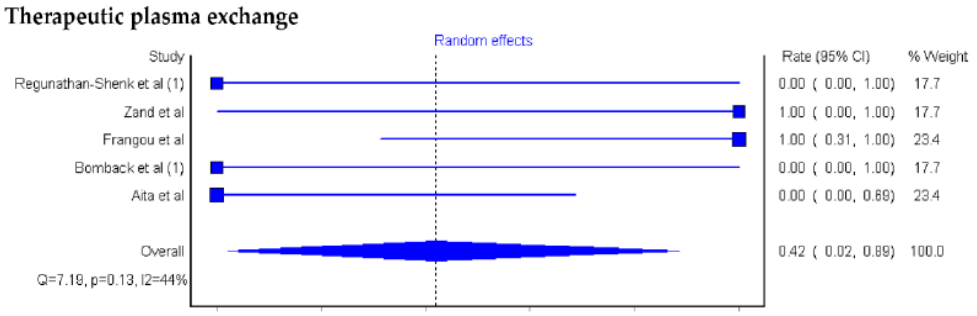


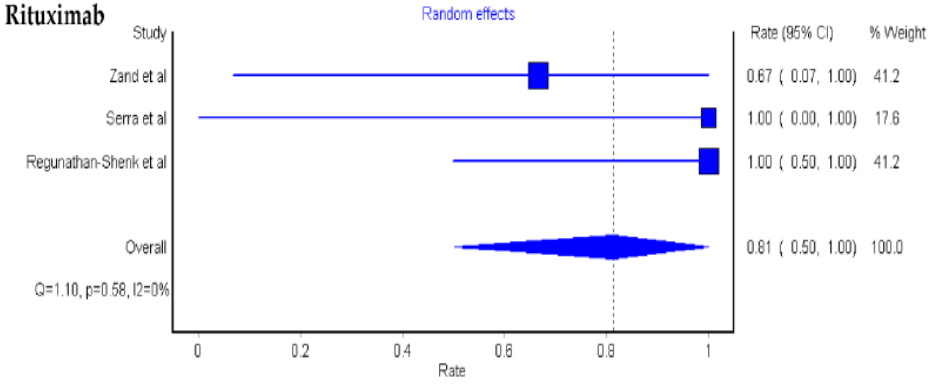


122 patients: (73 C3GN, 49 DDD)

- 33% tx loss after ecu
  - 22% C3GN and 53% DDD)
- 42% after TPE
- 81% after Ritux
- No Rx
  - 32% C3GN
  - 53% DDD

Gonzalez Suarez et al, Med. Sci 2020, 44

# Current Therapeutic Approach

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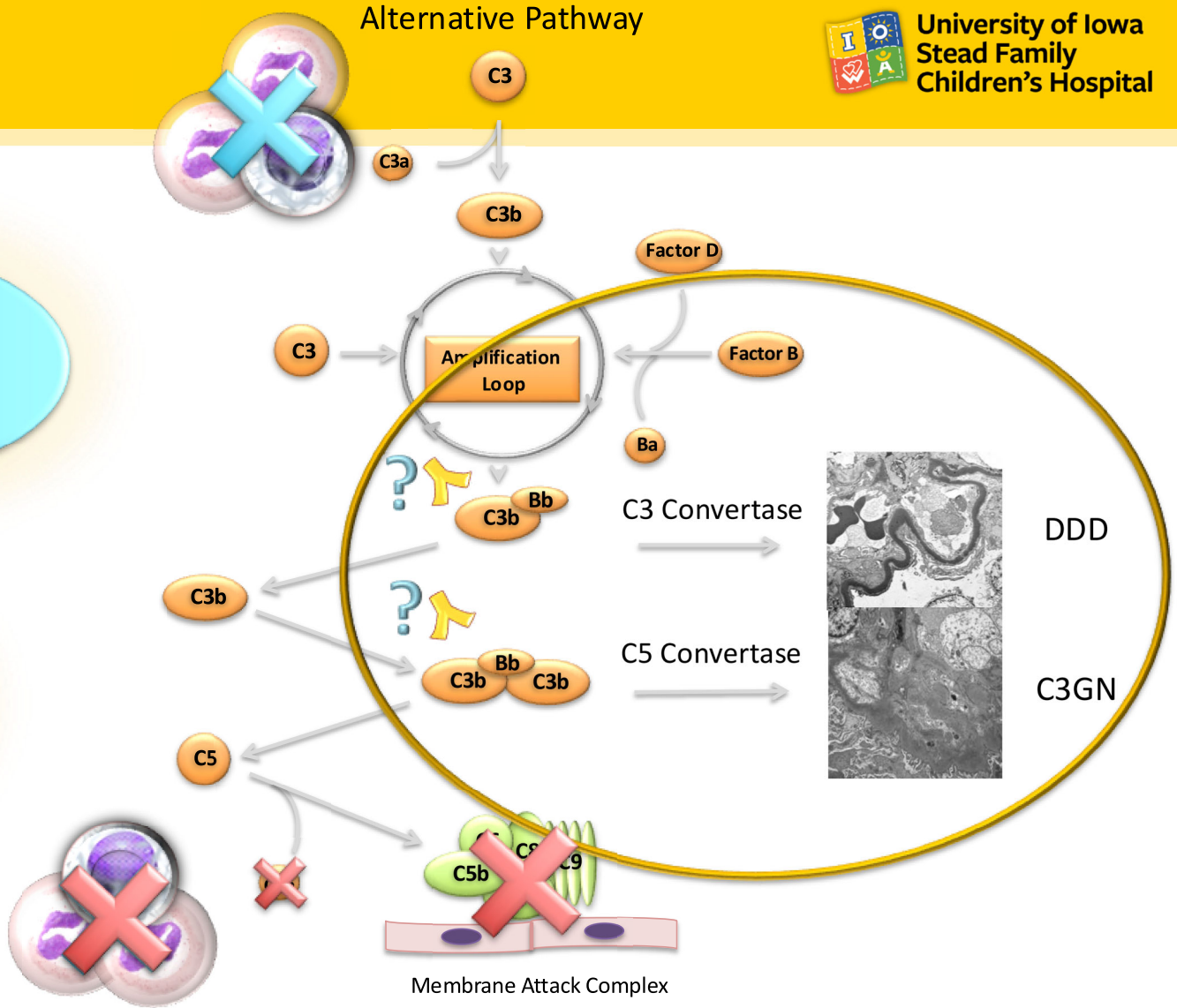
Steroids + Mycophenolate

Terminal Complement Blockade



# General rule of thumb for escalating care

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- Despite Current Cares:
  - Increasing urine protein (generally >1g/d) or creatinine
  - Advancing histology
  - Increasing symptoms
- Trial of at least 6 months of current cares
  - Lowest duration possible for steroids (ie ≤12 weeks in children)
- Inability to tolerate current cares

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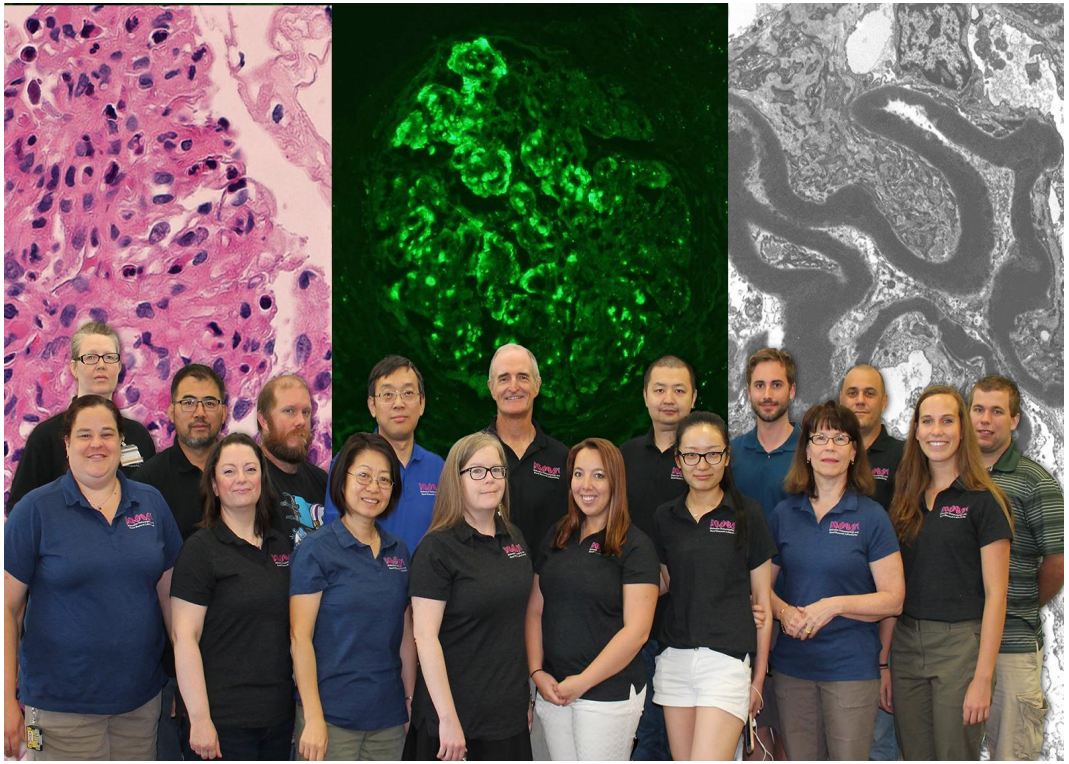
## Division of Pediatric Nephrology


## Molecular Otolaryngology and Renal Research Laboratory



**I'm very thankful to have Two "Work" Families**

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# Thank You

# Good Health To All!