C3 Glomerulopathy: role of complement for pathogenesis and treatment

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MPGN: the old classification...

**MPGN Type I**  
Subendothelial deposits  
West et al, J Pediatr 1965

**MPGN Type II / DDD**  
Intramembranous deposits  

**MPGN Type III**  
Subendothelial and subepithelial deposits  
Burkholder et al, Am J Pathol 1969  
Anders et al, Virchows Arch A Pathol Anat Histol 1997  
Strife et al, Clin Nephrol 1984
A new disease entity: C3GN

19 patients with unusual glomerulonephritis and:
- C3NeF positivity (7), CFH (3), CFI (2) or MCP (1) mutations
- overt mesangial and epimembranous C3 deposits
- absence of dense intramembranous deposits (no DDD)
- no Ig deposition
→ C3GN
Complement AP dysregulation in kidney diseases

- DDD/C3GN
- aHUS

C3Glomerulopathy

- Systemic
- Local

C3
- C5/MAC
Renal biopsy in C3G

Pickering et al, KI 2013: C3 at least 2-fold brighter than other IF
The distinction C3GN/DDD requires electron microscopy

Walker PD et al, Modern Pathol 2007

Evidence for a role of complement in DDD/C3GN in humans

- Proteomic profile of microdissected glomeruli: C3, C4, C5, C6, C7, C8, CFHR1, CFHR5....

- Very similar profile between DDD and C3GN

A simplified view of the complement system

Zipfel and Skerka, Nat Rev Immunol 2009
Different alternative pathway alterations lead to C3 glomerulopathies

C3 glomerulopathies

modified from Sethi S, Fervenza FC NEJM 2012
New classification of MPGN

Proliferative glomerulonephritis

Positive Igs +/− C3

Ig-mediated

− Monoclonal gammopathies
  Dysproteinemia

− Autoimmune diseases

− Infections

Negative Igs + C3

Complement-mediated

C3 Glomerulopathies

DDD

C3GN

Sethi S and Fervenza FC, Semin Nephrol 2011
Sethi S and Fervenza FC, NEJM 2012

*Servais et al, Kidney Int 2012; Dragon-Durey et al. JASN 2004;
IC-MPGN can also be secondary to dysregulation of the complement alternative pathway: C3Nef

## Table 3 | Complement component analysis and immunofluorescence study of membranoproliferative glomerulonephritis type I cases with positive C3 nephritic factor

<table>
<thead>
<tr>
<th>Patient</th>
<th>C3a (660 to 1250 mg/l)</th>
<th>C4a (90 to 380 mg/l)</th>
<th>CFBa (90 to 320 mg/l)</th>
<th>Histology</th>
<th>Immunofluorescence study</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>537b</td>
<td>160</td>
<td>83</td>
<td>MPGN I</td>
<td>IgG, IgM, C3</td>
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<tr>
<td>26</td>
<td>512</td>
<td>127</td>
<td>50</td>
<td>MPGN I</td>
<td>IgG, IgM, IgA, C3</td>
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<tr>
<td>27</td>
<td>183</td>
<td>178</td>
<td>225</td>
<td>MPGN I</td>
<td>IgG, C3</td>
</tr>
<tr>
<td>28</td>
<td>701</td>
<td>233</td>
<td>96</td>
<td>MPGN I</td>
<td>IgG, C3</td>
</tr>
<tr>
<td>29</td>
<td>87</td>
<td>202</td>
<td>51</td>
<td>MPGN I</td>
<td>IgG, IgM, C3</td>
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<tr>
<td>30</td>
<td>847</td>
<td>222</td>
<td>71</td>
<td>MPGN I</td>
<td>IgG, IgM, C3, C1q</td>
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<tr>
<td>31</td>
<td>48</td>
<td>126</td>
<td>89</td>
<td>MPGN I</td>
<td>IgG, IgA, C3</td>
</tr>
<tr>
<td>32</td>
<td>87</td>
<td>309</td>
<td>92</td>
<td>MPGN I</td>
<td>IgG, IgM, C3</td>
</tr>
<tr>
<td>33</td>
<td>293</td>
<td>209</td>
<td>100</td>
<td>MPGN I</td>
<td>IgG, IgM, C3</td>
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<tr>
<td>34</td>
<td>180</td>
<td>248</td>
<td>123</td>
<td>MPGN I</td>
<td>IgG, IgM, C3</td>
</tr>
<tr>
<td>35</td>
<td>193</td>
<td>95</td>
<td>126</td>
<td>MPGN I</td>
<td>IgG, C3</td>
</tr>
<tr>
<td>36</td>
<td>275</td>
<td>225</td>
<td>159</td>
<td>MPGN I</td>
<td>IgG, IgM, C3, C1q</td>
</tr>
<tr>
<td>37</td>
<td>1110</td>
<td>162</td>
<td>186</td>
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<td>NDc</td>
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<td>38</td>
<td>475</td>
<td>175</td>
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<td>IgG, C3</td>
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<tr>
<td>40</td>
<td>875</td>
<td>273</td>
<td>124</td>
<td>MPGN I</td>
<td>IgG, C3, C1q</td>
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<tr>
<td>41</td>
<td>135</td>
<td>182</td>
<td>130</td>
<td>MPGN I</td>
<td>IgG, IgA, IgM, C3</td>
</tr>
<tr>
<td>42</td>
<td>129</td>
<td>227</td>
<td>64</td>
<td>MPGN I</td>
<td>IgG, C3</td>
</tr>
</tbody>
</table>

Abbreviations: CFB, complement factor B; Ig, immunoglobulin; MPGN I, membranoproliferative glomerulonephritis type I; ND, not done.

*Laboratory reference values are indicated in brackets.

bRare variant CFI IVS 12+5 associated.

cBiopsy performed in 1974: lobular MPGN I, no immunofluorescence study available.

Cases with genetic abnormality are presented in Table 2.
IC-MPGN can also be secondary to dysregulation of the complement alternative pathway: genetic mutations

IC-MPGN can also be secondary to dysregulation of the complement alternative pathway: anti-FB and anti-C3b

Anti-Factor B and Anti-C3b Autoantibodies in C3 Glomerulopathy and Ig-Associated Membranoproliferative GN

Maria Chiara Marinozzi,† Lubka T. Roumenina,*,† Sophie Chauvet,*, Alexandre Hertig,† Dominique Bertrand,† Jérôme Olagne,‡ Marie Frimat,† Tim Ulinski,‡ Georges Deschênes,†§ Stephane Burtey,‖ Michel Delahousse,‖ Bruno Moulin,‡ Christophe Legendre,‡§ Véronique Frémoux Bacchi,‖ and Moglio Le Quintrec*†§

Table 1. Summary of the clinical characteristics of the patients

<table>
<thead>
<tr>
<th>Pt</th>
<th>Sex</th>
<th>Age at Onset, yr</th>
<th>Background</th>
<th>Ig-MPGN/C3G</th>
<th>Infectious Trigger</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>31</td>
<td>Drug/HBV</td>
<td>Ig-MPGN</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>34</td>
<td>Anorexia</td>
<td>Ig-MPGN</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>66</td>
<td></td>
<td>C3G</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>40</td>
<td>Myelofibrosis</td>
<td>Ig-MPGN</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>49</td>
<td>Myelofibrosis</td>
<td>Ig-MPGN</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>32</td>
<td>Myelofibrosis</td>
<td>C3G</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>7</td>
<td>Myelofibrosis</td>
<td>C3G</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>63</td>
<td>Alcohol/HBV</td>
<td>Ig-MPGN/C3G</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>9</td>
<td></td>
<td>C3G</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>55</td>
<td></td>
<td>Ig-MPGN</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>34</td>
<td></td>
<td>Ig-MPGN</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>38</td>
<td>Drug</td>
<td>Ig-MPGN</td>
<td>Yes</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>55</td>
<td>Crohn/B lymphoma</td>
<td>Ig-MPGN</td>
<td>Yes</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>32</td>
<td></td>
<td>Ig-MPGN</td>
<td>No</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>18</td>
<td></td>
<td>C3G</td>
<td>No</td>
</tr>
</tbody>
</table>

The CKD stages are defined by the level of kidney function according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.
The value of repeat biopsies

Patients with a «rich» IF who
1) do not respond as well as expected to standard immunosuppression and
2) maintain low circulating C3
may benefit from a repeat renal biopsy and screening for complement abnormalities

Positive C3Nef
Elevated C5b9
MCP mutation
What can we learn from the renal biopsy?

**C4d as a Diagnostic Tool in Proliferative GN**

Sanjeev Sethi,* Samih H Nasr,* An S. De Vries,† and Fernando C. Fervenza‡

*J Am Soc Nephrol 26: 1–8, 2015*

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**Proliferative glomerulonephritis**

- **Immune-complex mediated GN**
  - Ig ++/+++ C3 +/++/++++
  - C1q +/-/++++ C4d+++/++++
  - CP activation
    - Eg: Autoimmune disease, monoclonal Ig, infections*
  - LP activation
    - Eg: Infections, IgA nephropathy, membranous nephropathy, monoclonal Ig**

- **Complement-mediated GN**
  - C3 ++/+++ Ig 0/+ C1q 0/trace C4d +/++/++++
  - LP/CP activation, possibly in addition to AP
    - Eg: C3 glomerulopathy triggered by infections, autoimmune disease, monoclonal Ig***
  - AP activation
    - Eg: C3 glomerulopathy driven by AP abnormalities**
C4d staining does not exclude C3G
Extrarenal features

Partial lipodystrophy

Macula

Drusen

Lipids & proteins
C3G: clinical presentation is heterogenous

• Post-infectious glomerulonephritis with low C3

• Infection triggering macrohematuria, as in IgA nephropathy

• Nephrotic syndrome

• Accidental finding of non-nephrotic proteinuria, microhematuria

• Atypical
C3G presenting as acute PIGN

• Post-infectious glomerulonephritis with

1) low C3 that persists > 12 weeks or with
2) recurrent macrohematuria

Table 3: Complement abnormalities

<table>
<thead>
<tr>
<th>Patient</th>
<th>CFH</th>
<th>CFHRS</th>
<th>FH antibodies(^a)</th>
<th>Hemolytic assay(^b)</th>
<th>APFA(^c)</th>
<th>C3NeF</th>
<th>sMAC(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>c.2171delC, p.Thr724fsX, 725</td>
<td>No mutations</td>
<td>Negative</td>
<td>ND</td>
<td>ND</td>
<td>Negative</td>
<td>0.24 mg/l</td>
</tr>
<tr>
<td>2</td>
<td>No mutations</td>
<td>c.646-647, AA&gt;TT, p.Asn216Phe</td>
<td>Negative</td>
<td>0%, Normal</td>
<td>63%, Abnormal</td>
<td>Negative</td>
<td>0.21 mg/l</td>
</tr>
<tr>
<td>3</td>
<td>No mutations</td>
<td>No mutations</td>
<td>Negative</td>
<td>1%, Normal</td>
<td>63%, Abnormal</td>
<td>Positive (C3SAP(^f))</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>No mutations</td>
<td>No mutations</td>
<td>Negative</td>
<td>0%, Normal</td>
<td>1% Abnormal</td>
<td>Positive (IFE)</td>
<td>1.23 mg/l</td>
</tr>
<tr>
<td>5</td>
<td>No mutations</td>
<td>No mutations</td>
<td>Negative</td>
<td>12% Abnormal</td>
<td>34% Abnormal</td>
<td>Positive (IFE)</td>
<td>0.48 mg/l</td>
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<tr>
<td>6</td>
<td>No mutations</td>
<td>No mutations</td>
<td>Negative</td>
<td>0%, Abnormal</td>
<td>14% Abnormal</td>
<td>Positive (both assays)</td>
<td>ND</td>
</tr>
<tr>
<td>7</td>
<td>c.3350A&gt;G, p.Asn1175Ser</td>
<td>No mutations</td>
<td>Negative</td>
<td>0% Normal</td>
<td>80%</td>
<td>Negative</td>
<td>ND</td>
</tr>
<tr>
<td>8</td>
<td>No mutations</td>
<td>No mutations</td>
<td>Negative</td>
<td>0% Normal</td>
<td>123%</td>
<td>Negative</td>
<td>0.13 mg/l</td>
</tr>
<tr>
<td>9</td>
<td>No mutations</td>
<td>No mutations</td>
<td>Negative</td>
<td>9% Abnormal</td>
<td>77%</td>
<td>Positive (both assays)</td>
<td>ND</td>
</tr>
<tr>
<td>10</td>
<td>c.1699A&gt;G, p.Arg567Gly</td>
<td>No mutations</td>
<td>Negative</td>
<td>0%, Normal</td>
<td>0% Abnormal</td>
<td>Positive (both assays)</td>
<td>2.03 mg/l</td>
</tr>
<tr>
<td>11</td>
<td>No mutations</td>
<td>No mutations</td>
<td>Negative</td>
<td>0%, Normal</td>
<td>0%</td>
<td>Positive (C3SAP(^f))</td>
<td>0.21 mg/l</td>
</tr>
</tbody>
</table>

Sethi, Kidney International 2012
Atypical PIGN is a form of C3G

### Light microscopy

<table>
<thead>
<tr>
<th>Condition</th>
<th>PIGN</th>
<th>aPIGN</th>
<th>C3GN</th>
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</thead>
<tbody>
<tr>
<td>Diff. prol.</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Mes. prol.</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>MPGN</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Crescentic</td>
<td>+</td>
<td>+</td>
<td>-</td>
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### Immunofluorescence

<table>
<thead>
<tr>
<th>Condition</th>
<th>PIGN</th>
<th>aPIGN</th>
<th>C3GN</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3 capill.</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>C3 mesang.</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>IgG</td>
<td>++</td>
<td>+</td>
<td>+/-</td>
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</table>

### Electron microscopy

<table>
<thead>
<tr>
<th>Condition</th>
<th>PIGN</th>
<th>aPIGN</th>
<th>C3GN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humps</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Mesangial</td>
<td>+/-</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Sub-endoth.</td>
<td>+/-</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

Adapted from Sethi et al, Kidney International 2013
CFHR nephropathy: C3G presenting as “IgA nephropathy”

- Infection-triggered macrohematuria, proteinuria

**Identification of a mutation in complement factor H-related protein 5 in patients of Cypriot origin with glomerulonephritis**


Lancet 2010

1) CFHR protein mutation
2) Abnormal dimerization
3) FH deregulation

C3G can present as nephrotic syndrome

• Post-infectious glomerulonephritis with low C3

• Infection triggering macrohematuria, as in IgA nephropathy

• Nephrotic syndrome
A difficult case

- 13-year-old boy
- nephrotic syndrome & hematuria
- markedly low C3 and C4
- initial renal biopsy: MPGN with strong C3 deposition
  strong immunoglobulin deposition
- follow-up biopsies (1 and 3 years): MPGN with strong C3 deposition
  ± no immunoglobulin deposition
- Elevated sC5b-9
  treated with eculizumab: decrease in proteinuria

Kerns et al, Ped Nephrol 2013
C3G can be found on routine urinalysis

• Post-infectious glomerulonephritis with low C3

• Infection triggering macrohematuria, as in IgA nephropathy

• Nephrotic syndrome

• Accidental finding of non-nephrotic proteinuria, microhematuria
C3G can present as aHUS

- Post-infectious glomerulonephritis with low C3
- Infection triggering macrohematuria, as in IgA nephropathy
- Nephrotic syndrome
- Accidental finding of non-nephrotic proteinuria, microhematuria
- Atypical
INITIAL PRESENTATION: aHUS

A 5-year old child was transferred in May 2014 from the Cosenza Pediatric Department with HUS, requiring hemodialysis.

UPON ARRIVAL

He presented with slight confusion, severely hypertensive
- Hb 8.4 g/dl and 66,000 platelets/mmc
- terminal renal failure
- low C3 (51 mg/dl, normal range 90-180 mg/dl), with normal C4
- nephrotic-range proteinuria with red blood cells and casts in the urinary sediment
- stool culture and serum antibodies were negative for VTEC
- ADAMTS13 levels were slightly reduced (40%)

1) a full workup of complement mutations was performed
2) therapy with eculizumab was started
Following start of eculizumab, platelets rapidly increased and after 10 days hemodialysis was discontinued.

However, **renal function remained abnormal with proteinuria in the nephrotic range and persistently low circulating C3.**

Therefore, a renal biopsy was performed, which showed:

**Optic Microscopy:**
- **No sign of thrombotic microangiopathy, diagnostic of aHUS**
- Mesangial proliferation with increase in matrix
- Endocapillary proliferation and, in 25% of glomeruli, extracapillary proliferation
- Slight tubular atrophy

**Immunofluorescence with C3 ++, IgG +/-, fibrinogen +/-, negative IgA, IgM, C1q**

**Electron Microscopy:**
Subendothelial deposits with extensive remodeling of the glomerular capillary walls, signs of chronic damage of arteriolar walls and of chronic TMA
TREATMENT

• 3 i.v. methylprednisolone boluses followed by oral prednisone for 1 month, tapered until discontinuation at 6 months
• continued therapy with eculizumab for 9 months, 3 months after discontinuation of prednisone

This approach led to gradual complete normalization of renal function (in 5 months) and of proteinuria (in 3 months), normal circulating C3, normal complete blood count.

At 6 months a control renal biopsy was performed, showing a marked reduction in mesangial proliferation and in C3 positivity, but a significant sclerosis, global in 10-11/20 glomeruli, focal in 3-4/the remaining glomeruli.

Therapy with eculizumab was discontinued, and until now (30 months later) there is no sign of disease reactivation nor of increase in proteinuria.
Clinical, histological and molecular overlaps

**C3 glomerulopathies**

- Endocapillary
- Intramembranous
- Membrano- or mesangioprolif.

**Predominant but not exclusive C3 deposition**

Adapted from Zipfel et al, Molecular Immunology (2015)
### C3G: OPBG experience on 32 pediatric patients

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Urine</th>
<th>Biopsy</th>
<th>Therapy</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>(number of patients)</td>
<td>M.E.</td>
<td>C3GN</td>
<td>DDD</td>
<td>None</td>
</tr>
<tr>
<td>Acute PIGN (13)</td>
<td>100%</td>
<td>92%</td>
<td>8%</td>
<td>31%</td>
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<td>77%</td>
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<tr>
<td></td>
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<td>91%</td>
<td>9%</td>
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<td>55%</td>
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<tr>
<td>Random urine (8)</td>
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<td>50%</td>
<td>50%</td>
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</tbody>
</table>
C3 glomerulopathy outcome: Servais

Table 1 | Clinical and biological data according to histological type

<table>
<thead>
<tr>
<th></th>
<th>ALL</th>
<th>MPGN 1</th>
<th>DDD</th>
<th>GNC3</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>134</td>
<td>49</td>
<td>29</td>
<td>56</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>81/53 (60.4%)</td>
<td>32/17 (65.3%)</td>
<td>17/12 (58.6%)</td>
<td>33/24 (58.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Children/adults</td>
<td>52/82 (38.8%)</td>
<td>21/28 (42.8%)</td>
<td>17/12 (58.6%)</td>
<td>14/42 (25.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>24.3 ± 18.6</td>
<td>20.7 ± 16.8</td>
<td>18.9 ± 17.7</td>
<td>30.3 ± 19.3</td>
<td>&lt;0.05^c and &lt;0.01^d</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>4.9 ± 4.1</td>
<td>6.9 ± 4.4</td>
<td>5.6 ± 4.5</td>
<td>3.6 ± 3.3</td>
<td>&lt;0.05^c</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>58 (41.1%)</td>
<td>32 (65.3%)</td>
<td>11 (37.9%)</td>
<td>15 (26.8%)</td>
<td>&lt;0.0001^e and 0.02^e</td>
</tr>
<tr>
<td>Microhematuria</td>
<td>83 (58.8%)</td>
<td>25 (51.0%)</td>
<td>22 (75.8%)</td>
<td>36 (64.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>HBP</td>
<td>43 (30.5%)</td>
<td>16 (32.6%)</td>
<td>6 (20.7%)</td>
<td>21 (37.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m^3)</td>
<td>69.3 ± 36.6</td>
<td>73.7 ± 33.7</td>
<td>75.5 ± 38.8</td>
<td>65.9 ± 37.4</td>
<td>NS</td>
</tr>
<tr>
<td>ACE inhibitor/ARB treatment</td>
<td>64 (45.4%)</td>
<td>27 (55.1%)</td>
<td>10 (34.5%)</td>
<td>27 (48.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Immunosuppressive treatment</td>
<td>61 (43.2%)</td>
<td>28 (57.1%)</td>
<td>14 (48.3%)</td>
<td>19 (33.9%)</td>
<td>0.02^c</td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>11.2 ± 11.2</td>
<td>11.7 ± 12.0</td>
<td>12.0 ± 12.1</td>
<td>10.2 ± 10.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

At last follow-up

- eGFR (ml/min per 1.73 m^3) 50.4 ± 39.5
- Proteinuria (g/day) 2.2 ± 2.7
- Nephrotic syndrome 19 (14.1%)
- Duration of evolution until ESRD^b (years) 10.3 ± 10.2
- Dialysis 49 (36.6%)
- Age at dialysis (years) 35.6 ± 17.6
- Renal transplantation 35 (26.1%)
  - Recurrence 18 (51.4%)
  - Thrombotic microangiopathy 6 (17.1%)
  - Vascular rejection 2 (5.8%)
Risk factors of poor long-term outcome in C3G

Multivariate analysis of the association of long-term renal outcome with clinical, laboratory and genetic features.

<table>
<thead>
<tr>
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<th>All patients</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
</tr>
<tr>
<td>Absence of mutations or C3NeFs</td>
<td>7.1</td>
</tr>
<tr>
<td>Sclerotic glomeruli (% of glomeruli)</td>
<td>69.3</td>
</tr>
<tr>
<td>Crescents (% of glomeruli)</td>
<td>39.7</td>
</tr>
<tr>
<td>Nephrotic syndrome at onset</td>
<td>10.9</td>
</tr>
</tbody>
</table>

HR: hazard ratio calculated by Multivariate Cox proportional-Hazards analysis. CI: confidence Interval. nc: not calculable. Nephrotic syndrome was defined as: 24-h proteinuria exceeding 3.5 g in adults or 40 mg/h/m2 in children together with albuminemia ≤3 g/dL. Intensified immunosuppression was also included in multivariate Cox Regression analysis but was not significantly associated with progress to ESRD (HR = 3.9, 95%CI 0.65–23.9, p = 0.138).
How to treat C3G?

Inflammation!
Effectiveness of mycophenolate mofetil in C3 glomerulonephritis

Cristina Rabasco¹, Teresa Caver³, Elena Román³, Jorge Rojas-Rivera³, Teresa Olea⁴, Mario Espinosa⁵, Virginia Cabello⁶, Gema Fernández-Juarez⁷, Fayna González⁸, Ana Ávila⁹, José María Baltar¹⁰, Montserrat Díaz¹¹, Raquel Alegre¹², Sandra Elías¹², Monserrat Antón¹³, Miguel Angel Frutos¹⁴, Alfonso Pobes¹⁵, Miguel Blasco¹⁶, Francisco Martín¹⁷, Carmen Bernis¹⁸, Manuel Macías¹⁹, Sergio Barroso²⁰, Alberto de Lorenzo²¹, Gema Ariceta²², Manuel López-Mendoza²³, Begoña Rivas²⁴, Katia López-Revuelta²⁵, José María Campistol²⁶, Santiago Mendizábal²⁷, Santiago Rodríguez de Córdoba²³ and Manuel Praga¹,²⁴ for the Spanish Group for the Study of Glomerular Diseases (GLOSEN)

Effectiveness of mycophenolate mofetil in C3 glomerulonephritis

Renal survival (defined by a status free of end-stage renal disease) in patients treated with MMF (MMF-IST), other IST (other-IST), and no IST (non-IST). ESRD, end-stage renal disease; IST, immunosuppressive treatments; MMF, mycophenolate mofetil.

Figure 1: Renal survival (free of ESRD status) in patients treated with MMF (MMF-IST), other IST (other-IST), and no IST (non-IST) during follow-up. The survival curves show that patients treated with MMF-IST have a higher renal survival rate compared to those treated with other IST or no IST.
Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference


Table 5 | Recommended treatment approach for C3G

| All patients | Optimal blood pressure control (suggested blood pressure below the 90th in children and ≤120/80 mm Hg in adults) |
| Moderate disease | 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 |
| Severe disease | 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
- Prednisone
- Mycophenolate mofetil
- 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
*Based on a single, small prospective trial, case reports, and expert opinion.
Complement-targeting therapies: anti-C5 blocks the terminal complement pathway
Treatment of DDD with anti-C5 (eculizumab)

ATTENTION:

- not all patients respond so well
- it may work better in those with elevated sC5b9
- expensive and there is a risk of meningococcal infection
Circulating C3 and C5b-9 according to renal histology

C3 convertase dysregulation:  
DDD>C3GN

C5 convertase dysregulation:  
C3GN>DDD

Servais et al, Kidney Int 2012

Yuzhou Zhang et al. CJASN 2014
Complement-targeting therapies on the horizon

**DISEASE**
- IC-MPGN
- C3G
- IgAN
- IMN

**COMPLEMENT-TARGETING THERAPIES**
- Soluble CR1
- Anti-Factor B
- Anti-Factor D
- Anti- Properdin
- Anti-C3 (Compsstatin)
- Aurin tricarboxylic acid

**AAV**
- GPA

**aHUS**
- Anti-C5
- C5 siRNA
- C5aR antagonist (CCX168)
- Anti-C5a
- Anti-C5
- Aurin tricarboxylic acid
1) Complement involvement is being found in a growing number of kidney diseases

• Permanent (genetic) as in aHUS, genetic forms of C3G

• Transitory (infectious trigger) as in PIGN

• Concomitant to an immune-mediated mechanism such as in antibody-mediated C3G, IC – MPGN, lupus nephritis, AAV / GPA, IgAN, MN, APL, humoral rejection

2) C3G is extremely heterogenous and less rare than we thought. Some cases may spontaneously improve. Some patients have a relapsing course.

3) Treatment of C3G should be tailored on a pathogenetic basis to target the involved mediator. Immunosuppressive drugs (PDN, MMF) may be beneficial both to treat the immune-mediated mechanism, if present, and if there is evidence of renal inflammation

4) Anti-C5 therapy may be beneficial in some, but not in all patients
THANK YOU

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• Prof Christoph Licht

• Dr Marina Noris
• Dr Elena Bresin
• Dr Veronique Fremeaux-Bacchi

• Prof Francesco Emma

The patients and their families