CONTROVERSIES CONFERENCE ON GLOMERULAR DISEASE

MPGN AND C3G

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University of Iowa
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I have no disclosures relevant to today’s presentation. The following includes a list of recent affiliations:

<table>
<thead>
<tr>
<th>Affiliation / Financial Interest</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016 – Consultant</td>
<td>Achillion Pharmaceuticals</td>
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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/](https://coi.research.uiowa.edu/)
Objectives

• Summarize the state of the literature pertaining to topic

• Identify new and important questions or controversies related to diagnosis and management of these diseases

• Explain why these topics are controversial

• Evaluate the data supporting opinions related to these questions/controversies

• Discuss what types of studies would help to move the field forward with regards to these questions
Historical Perspective

Chapter 8 - Idiopathic Membranoproliferative Glomerulonephritis

• “Light microscopic pattern of injury”
• “Further classified based on the extent and location of deposits” (I, II, and III)
• “Heterogeneity of cause”
• “Truly idiopathic MPGN is now a very uncommon condition”
• “Those in which C3 is exclusively deposited are known as C3GN”.
• “Treatment is highly dependent on proper identification of underlying cause.”
Etiologic Perspective

- Biopsy diagnoses - defined primarily by the character/location of deposits
  - MPGN: Pattern of injury with multiple causes.
  - C3G: Abnormal complement role (with no way to rule out "normal" complement activity)
Definition of C3 Glomerulopathy

C3 glomerulopathy: consensus report

Matthew C. Pickering¹, Vivette D. D’Agati², Carla M. Nester³,⁴, Richard J. Smith³,⁴, Mark Haas⁵, Gerald B. Appel⁶, Charles E. Alpers⁷, Ingeborg M. Bajema⁸, Camille Bedrosian⁹, Michael Braun¹⁰, Mittie Doyle⁹, Fadi Fakhouri¹¹, Fernando C. Fervenza¹², Agnes B. Fogo¹³, Véronique Frémeaux-Bacchi¹⁴, Daniel P. Gale¹⁵, Elena Goicoechea de Jorge¹, Gene Griffin⁹, Claire L. Harris¹⁶, V. Michael Holers¹⁷, Sally Johnson¹⁸, Peter J. Lavin¹⁹, Nicholas Medjeral-Thomas¹, B. Paul Morgan¹⁶, Cynthia C. Nast⁵, Laure-Hélène Noel²⁰, D. Keith Peters²¹, Santiago Rodríguez de Córdoba²², Aude Servais²³, Sanjeev Sethi²⁴, Wen-Chao Song²⁵, Paul Tamburini⁹, Joshua M. Thurman¹⁷, Michael Zavros²⁶ and H. Terence Cook¹

“.......... designates a disease process due to abnormal control of complement activation, deposition, or degradation and characterized by predominant glomerular C3 fragment deposition..........”

Role of Biomarkers
• Target Identifiers?
• Outcomes Signals?
Complement and the Kidney

Complement Mediated Renal Disease

- C3G
- TMA
- MPGN
- ?
MPGN and C3G: Spectrum?

<table>
<thead>
<tr>
<th></th>
<th>MPGN</th>
<th>DDD</th>
<th>C3GN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>20.7±16.8</td>
<td>18.9±17.7</td>
<td>30.3±19.3</td>
</tr>
<tr>
<td>Nephrotic Syndrome</td>
<td>65.3%</td>
<td>37.9%</td>
<td>26.8%</td>
</tr>
<tr>
<td>Dialysis</td>
<td>40.8%</td>
<td>41.4%</td>
<td>30.3%</td>
</tr>
<tr>
<td>Recurrence in Tx</td>
<td>42.8%</td>
<td>54.5%</td>
<td>60%</td>
</tr>
<tr>
<td>Low C3</td>
<td>46.3%</td>
<td>59.1%</td>
<td>39.6%</td>
</tr>
<tr>
<td>Low Factor B</td>
<td>34.1%</td>
<td>27.3%</td>
<td>26.4%</td>
</tr>
<tr>
<td>Low Factor H</td>
<td>4.9%</td>
<td>18.2%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Low Factor I</td>
<td>7.3%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C3Nef</td>
<td>53.6%</td>
<td>86.4%</td>
<td>45.3%</td>
</tr>
<tr>
<td>CFH Mutations</td>
<td>10.4%</td>
<td>17.2%</td>
<td>12.5%</td>
</tr>
<tr>
<td>CFI Mutations</td>
<td>6.2%</td>
<td>0</td>
<td>5.3%</td>
</tr>
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</table>

8.1: Evaluation of MPGN
8.1.1: Evaluate patients with the histological (light microscopic) pattern of MPGN for underlying diseases before considering a specific treatment regimen (see Table 20). (Not Graded)

Table 20 | Underlying conditions associated with a membranoproliferative pattern of GN

- Chronic infections (especially hepatitis C)
- Autoimmune diseases (especially LN)
- Monoclonal gammopathies (especially light-chain deposition disease and monoclonal IgG disease)
- Complement dysregulation (especially complement factor H deficiency)
- Chronic and healed thrombotic microangiopathies
Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference


## Complement Investigations

### Tests recommended for all patients

- Measurement of serum C3 and C4
- Measurement of C3 Nephritic Factor
- Measurement of serum factor H
- Serum paraprotein ecalutation
- Screening for CFHR5 mutaton

### Tests that should be considred on a case-by-case basis as they require expert interpretation and/or clinical validation

- Measurement of serum factor B
- Measurement of serum C5
- Measurement of markers of C3 Activation
  - C3d, C3c, C3adesArg
- Measurement of C5 activation
  - Soluble C5b-9
- Measurement of FH autoantibodies
- Measurement of FB autoantibodies
- Mutation Screening of complement regulatory genes/activation genes
  - CFH, CFI, CD46/C3, CFB
- Assessment of Copy Number cariants across the CFH-CFHR locus
The Challenge

Devising diagnostic and treatment approaches when heterogeneity prevails
Background: KDIGO Guidelines

8.2: Treatment of idiopathic MPGN
8.2.1: We suggest that adults or children with presumed idiopathic MPGN accompanied by nephrotic syndrome AND progressive decline of kidney function receive oral cyclophosphamide or MMF plus low-dose alternate-day or daily corticosteroids with initial therapy limited to less than 6 months. (2D)
### Table 2. Treatment failure

<table>
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<tr>
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<th>Prednisone</th>
<th>Lactose</th>
<th>Fisher’s exact</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>one-tailed</td>
</tr>
<tr>
<td>All patients (n = 80)</td>
<td>16/44</td>
<td>18/33</td>
<td>0.087</td>
</tr>
<tr>
<td>Status known</td>
<td>19/47</td>
<td>–</td>
<td>0.154</td>
</tr>
<tr>
<td>Including 3 status</td>
<td>11/33</td>
<td>–</td>
<td>0.054</td>
</tr>
<tr>
<td>Types I, III (n = 59)</td>
<td>9/31</td>
<td>15/26</td>
<td>0.028</td>
</tr>
<tr>
<td>Status known</td>
<td>11/33</td>
<td>–</td>
<td>0.054</td>
</tr>
<tr>
<td>Including 3 status</td>
<td>11/33</td>
<td>–</td>
<td>0.054</td>
</tr>
<tr>
<td>Type II (n = 14)</td>
<td>5/9</td>
<td>3/5</td>
<td>0.657</td>
</tr>
<tr>
<td>Status known</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type unknown (n = 7)</td>
<td>2/4</td>
<td>0/2</td>
<td>0.400</td>
</tr>
<tr>
<td>Status known</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Including 1 status</td>
<td>3/5</td>
<td>–</td>
<td>0.286</td>
</tr>
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### Background

RCTs of well characterized patients are needed.


| All Patients | • Optimal blood pressure control (Suggested: BP below the 90% in children and <120/80 in adults)  
| | o Priority agents include angiotensin converting enzyme inhibitors and angiotensin receptor blockers,  
| | • Optimal nutrition for both normal growth in children, healthy weight in adults  
| | • Lipid control |

| Moderate Disease | Description  
| | • Urine protein over 500mg/24 hours despite supportive therapy or  
| | • Moderate inflammation on renal biopsy or  
| | • Recent increase in serum creatinine suggesting risk for progressive disease  
| | **Recommendation**  
| | • Prednisone  
| | • Mycophenolate mofetil |

| Severe Disease | Description  
| | • Urine protein over 500mg/24 hours despite supportive therapy  
| | • Or Moderate inflammation on renal biopsy  
| | • Or recent increase in serum creatinine suggesting risk for progressive disease  
| | **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. |
Complete Remission 2/20 (40%)  6/22 (32%)  5/18 (56%)
Partial Remission 3/20 (60%)  13/22 (68%)  4/18 (44%)
ESRD  10/20 (35%)  0/22 (0%)  3/18 (16%)
<table>
<thead>
<tr>
<th>#</th>
<th>Status</th>
<th>Description</th>
<th>Condition</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Active, not recruiting</td>
<td>Eculizumab in Primary MPGN</td>
<td>Membranoproliferative Glomerulonephritis</td>
<td>Drug: Eculizumab</td>
</tr>
<tr>
<td>2</td>
<td>Recruiting</td>
<td>A Proof-of-Mechanism Study to Determine the Effect of ACH-0144471 on C3 Levels in Patients With C3G or IC-MPGN</td>
<td>C3 Glomerulonephritis Dense Deposit Disease Membranoproliferative Glomerulonephritis, Type II (and 2 more...)</td>
<td>Drug: ACH-0144471</td>
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<tr>
<td>3</td>
<td>Not yet recruiting</td>
<td>Effect of Rituximab in Treatment of Membranoproliferative Glomerulonephritis</td>
<td>Membranoproliferative Glomerulonephritis</td>
<td>Drug: Rituximab Drug: Cyclosporin</td>
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<td>4</td>
<td>Recruiting</td>
<td>Daratumumab in Treatment of PGNMID and C3 GN</td>
<td>Membranoproliferative Glomerulonephritis</td>
<td>Drug: Daratumumab</td>
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<tr>
<td>5</td>
<td>Completed</td>
<td>Pilot Study of Rituximab for Membranoproliferative Glomerulonephritis</td>
<td>Glomerulonephritis, Membranoproliferative</td>
<td>Drug: Rituximab</td>
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<tr>
<td>6</td>
<td>Unknown †</td>
<td>Eculizumab Therapy for Dense Deposit Disease and C3 Nephropathy</td>
<td>Dense Deposit Disease Membranoproliferative Glomerulonephritis</td>
<td>Drug: Eculizumab</td>
</tr>
<tr>
<td>7</td>
<td>Recruiting</td>
<td>Controlled Trial Evaluating Avacopan in C3 Glomerulopathy</td>
<td>C3 Glomerulopathy (C3G)</td>
<td>Drug: Avacopan Drug: Avacopan Matching Placebo</td>
</tr>
</tbody>
</table>
Controversy

- Do we understand enough of the natural history of disease, or the variability in the phenotype?
- Do the differences in pathology signify an important phenotypic characteristic?
- Is complement "primary"/critical to the etiology of each of the diseases in the spectrum?
- Can the diagnosis (or activity) of either be secured with "biomarkers"?
  - What about genetics?
- Must we define disease more precisely in order to treat effectively?
Controversy

• Can we recommend a clinically/therapeutically important workup?
• What is “Idiopathic” MPGN?
• Is it time for us to say ICGN?