Mayo Clinic/ RPS Consensus Report on Classification, Diagnosis, and Reporting of Glomerulonephritis

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Disclosure

Relevant Financial Relationships
None

Off-Label/Investigational Uses
None

Learning Objectives

• Medical Knowledge
• Patient Care
• Practice-Based Learning and Improvement
The elephant that is Glomerulonephritis

By-Dr. D. Cattran, Toronto
What happens in glomerulonephritis (GN)

• Deposition of *injurious elements* along the glomerular capillary walls......Ig, complement, fibrin...

• Leads to inflammation- proliferative changes

• Followed by *healing/resolving* - leads to remodeling of the capillary walls, sclerosis, scarring........end stage kidney disease
Inflammation leads to patterns of injury: pathologist viewpoint is very “pattern-centric”

- **Mesangial proliferative glomerulonephritis**
- **Diffuse (exudative or endocapillary) proliferative glomerulonephritis**
- **Crescentic and necrotizing glomerulonephritis**
- **Membranoproliferative glomerulonephritis**
- **Sclerosing glomerulonephritis**
Glomerulonephritis

- Over the last 10-15 years we have made remarkable progress in understanding the etiology and pathophysiology of glomerulonephritis.

- This is very relevant to the evaluation, management, and prognosis of glomerulonephritis.

- Sometimes, this progress and understanding does not spill over into the kidney biopsy pathology report.

- There was a need to come up with a basic consensus document to address this issue.
Two simple questions

• We need to address the basic classification of GN based on etiology/pathophysiology

• How do we incorporate this into the pathology report:
  • Logical
  • Sequential
  • Reproducible
  • And most importantly address the key clinical questions
MPGN – a simple classification

MPGN

Positive Igs +/- C3

- Ig-mediated (including cryoglobulins)
  - Dysproteinemia
  - Autoimmune diseases
  - Infections

MPGN type I and III

Negative Igs + C3

- Dysregulation of the AP cascade
  - DDD
  - C3G

C3 Glomerulopathy

Membranoproliferative Glomerulonephritis — A New Look at an Old Entity

Sanjeev Sethi, M.D., Ph.D., and Fernando C. Fervenza, M.D., Ph.D.

Sethi, Fervenza
Seminars of Nephrology, 2011
Etiology-Based Diagnostic Approach to Proliferative Glomerulonephritis

Sanjeev Sethi, MD, PhD
• Thinking about it for 2-3 years, the more I travelled the more I felt the need but......
• Met with Lorraine Racusen and Mark Haas, Mysore, India, Aug 2014

• Came back and ran it by Fernando Fervenza. Basically asked him for the money.
November 2014, ASN, Philadelphia

- Called Helmut Rennke
- Lorraine Racusen and Michael Mengel - Lunch
- Sundaram Hariharan/Surya Seshan/Neeraja
- Terry Cook/Ian Roberts
- Tony Chang/Agnes Fogo/Ingeborg/Charlie Alpers
- Vivette D’Agati/Glen Markowitz
- Dick Glassock/Jai/Jerry/Dan Cattran
- The ones that got away - email - Charles Jennette, Pierre Ronco, Chris Winearls, Brad Rovin…….
Agenda

9:00 - 9:15 am  Welcome – Fernando C. Fervenza, MD, PhD
                Morning session chaired by Agnes Fogo, MD

9:15 - 9:45 am  What do the nephrologists want to see in the biopsy report
                Richard Glassock, MD

10:00 - 10:30 am Introduction, purpose and basic proposal –
                 Sanjeev Sethi, MD, PhD

10:30 - 11:00 am Should we include well defined entities –
                 Mark Haas, MD, PhD

11:00 - 11:30 am Complement testing: Relevance and when and what to order –
                 Richard Smith, MD

11:30 - 12 noon  The Banff experience – Michael Mengel, MD

Noon - 1:00 pm  Lunch

Afternoon session chaired by Helmut Rennke, MD

1:00 - 3:00 pm  Small group discussion on guidelines/discussion: (60-90 minutes
discussion, followed by 10 minutes/report: total 120-150 minutes)
- Guidelines for immunofluorescence microscopy and reporting (Pathogenesis) (What is a positive IF, scoring system, false positive and negatives, Indeterminate/overlap/difficult to classify group)
- Guidelines for electron microscopy and reporting
- Guidelines for the final report (the content and order)
- Guidelines for the use of ancillary studies (lymphocyte marker studies, in situ hybridization, spectrometry, special stains, antigen retrieval and unmasking, C4d, IgG subtypes, etc.)
- Guidelines on nomenclature: the pathogenesis/patterns of injury/etiology/disease entities
- Guidelines on chronicity: Glomerulosclerosis, IFTA and vascular lesions
- Clinical aspects in report: guide to evaluation/treatment

3:00 - 3:30 pm  Tea break
3:30 - 4:30 pm  Open hour for discussion
4:30 - 5:00 pm  Summary
Sanjeev Sethi, MD, PhD and Fernando C. Fervenza, MD, PhD
Glomerulonephritis Consensus Meeting

February 19 and 20, 2015
Mayo Clinic | Rochester, Minnesota
# Classification of Glomerulonephritis

<table>
<thead>
<tr>
<th>Pathogenic type</th>
<th>Specific Disease entity</th>
<th>Pattern of injury: focal or diffuse</th>
<th>Scores or class</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune-complex GN</strong></td>
<td>IgA nephropathy, IgA vasculitis, lupus nephritis, infection-related GN</td>
<td>Mesangial, endocapillary, exudative, membrano-, proliferative, necrotizing, crescentic, sclerosing or multiple*</td>
<td>- Oxford/MEST scores for IgA nephropathy</td>
</tr>
<tr>
<td></td>
<td>fibrillary GN with polyclonal Ig deposits</td>
<td></td>
<td>- ISN/RPS class for lupus nephritis</td>
</tr>
<tr>
<td><strong>Pauci-immune GN</strong></td>
<td>MPO-ANCA GN, PR3-ANCA GN, ANCA-negative GN</td>
<td>Necrotizing, crescentic, sclerosing or multiple*</td>
<td>Focal, crescentic, mixed or sclerosing class (Berden/ EUVAS class)</td>
</tr>
<tr>
<td><strong>Anti-GBM GN</strong></td>
<td>Anti-GBM GN</td>
<td>Necrotizing, crescentic, sclerosing or mixed*</td>
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<tr>
<td><strong>Monoclonal Ig GN</strong></td>
<td>Monoclonal Ig deposition disease, proliferative GN with monoclonal Ig deposits,</td>
<td>Mesangial, endocapillary, exudative, membrano-, proliferative, necrotizing, crescentic, sclerosing or multiple*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>immunotactoid glomerulopathy, fibrillary GN with monoclonal Ig deposits</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>C3 glomerulopathy</strong></td>
<td>C3 glomerulonephritis, dense deposit disease</td>
<td>Mesangial, endocapillary, exudative, membrano-, proliferative, necrotizing, crescentic, sclerosing or multiple*</td>
<td></td>
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</tbody>
</table>
Primary diagnosis

- Disease entity/pathogenic type
- Pattern of injury
- Scores/class/grade
- Additional features:
  - Clinical modifiers
  - Extent of chronic changes: glomerulosclerosis/IFTA/arteriosclerosis
Secondary diagnosis - some examples

- Diabetic nephropathy
- Thin GBM
- ATN
- Interstitial nephritis
| (1) Specimen type: needle biopsy, wedge, etc. |
| (2) Diagnosis |
| Primary diagnosis |
| Disease process/pathogenic type (e.g., IgA nephropathy, lupus GN, ANCA GN, C3 GN) |
| Pattern of glomerular injury (e.g., mesangial proliferative, membranoproliferative, necrotizing/crescentic, and focal and segmental sclerosing) |
| Histologic scores or grade (e.g., Oxford/MEST for IgA nephropathy and ISN/RPS for lupus nephritis) |
| Additional features (e.g., degree of global glomerulosclerosis, IFTA, vascular sclerosis, clinical modifiers, such as cryoglobulin/clinical HCV, bacterial endocarditis/clinical, staphylococcal cellulitis/clinical) |
| Secondary diagnoses (list; e.g., acute interstitial nephritis and diabetic glomerulosclerosis); these are not felt to be part of the primary disease |
| (3) Comment/narrative |
| Can be used for summarizing/clarifying morphologic basis of primary and/or secondary diagnoses or clinicopathologic correlations, providing prognostic information, discussing differential diagnosis, and providing appropriate references |
| (4) Summary of clinical data |
| (5) Gross description |
| (6) LM description |
| (7) IF/IHC |
| (8) EM |
| (9) Addendum for special studies |

MEST, mesangial hypercellularity, endocapillary hypercellularity, segmental sclerosis, interstitial fibrosis/tubular atrophy; ISN/RPS, International Society of Nephrology/Renal Pathology Society; EUVAS, European vasculitis study group; HCV, hepatitis C virus.
### Table 5. Guidelines for LM

<table>
<thead>
<tr>
<th>Glomeruli</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of glomeruli, including no. of globally and segmentally sclerosed and ischemic glomeruli</td>
</tr>
<tr>
<td>Focal versus diffuse and segmental versus global findings</td>
</tr>
<tr>
<td>Hypercellularity: mesangial, endocapillary, or exudative</td>
</tr>
<tr>
<td>Crescents: no./percentage, type (cellular, fibrocellular, or fibrous), and size (segmental or circumferential)</td>
</tr>
<tr>
<td>Fibrinoid necrosis and karyorrhexis</td>
</tr>
<tr>
<td>Wire loops, pseudo-(hyaline) microthrombi, and fibrin thrombi</td>
</tr>
<tr>
<td>Mesangial matrix expansion and presence of mesangiolyis</td>
</tr>
<tr>
<td>GBM thickening/thinning, double-contour formation, and other GBM abnormalities (e.g., spikes)</td>
</tr>
<tr>
<td>Disruption of GBM</td>
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<tr>
<td>Disruption of Bowman’s capsule</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Tubules and interstitium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial inflammation: type of infiltrate and location</td>
</tr>
<tr>
<td>Casts, crystals, and cysts</td>
</tr>
<tr>
<td>Acute tubular injury</td>
</tr>
<tr>
<td>Tubular basement abnormalities</td>
</tr>
<tr>
<td>IFTA: absent, mild, moderate, or severe</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vessels</th>
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</thead>
<tbody>
<tr>
<td>Arteritis, emboli, and thrombosis</td>
</tr>
<tr>
<td>Arteriosclerosis and arteriolosclerosis: absent, mild, moderate, or severe</td>
</tr>
</tbody>
</table>

### Table 6. Guidelines for IF

<table>
<thead>
<tr>
<th>No. of glomeruli, including no. of globally sclerosed glomeruli or with other evident lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity of staining: negative, ±, 1+, 2+, and 3+</td>
</tr>
<tr>
<td>Staining pattern: granular, linear, semilinear, smudgy, and linear accentuation</td>
</tr>
<tr>
<td>Location: focal or diffuse, segmental or global, mesangial, glomerular capillary wall, or both</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interstitial and tubular basement membrane staining: if present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segmental trapping of C3 and IgM is common in areas of segmental sclerosis or scarring: segmental glomerular tuft or coarse segmental staining</td>
</tr>
</tbody>
</table>

| Internal controls: albumin along TBM and GBM, C3 in vessels, and polyclonal IgA casts in tubules |

| TBM, tubular basement membrane. |

### Table 7. Guidelines for EM

<table>
<thead>
<tr>
<th>No. of glomeruli studied by EM, including no. globally sclerosed or with other evident lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular deposits: location, type, quantity, size, and substructure</td>
</tr>
<tr>
<td>GBM: architecture, thin/thick, duplication, ischemic changes, and rupture</td>
</tr>
<tr>
<td>Endothelium: fenestrations, swelling, and presence of tubuloreticular inclusions</td>
</tr>
<tr>
<td>Mesangial matrix: normal/increased and mesangiolyis</td>
</tr>
<tr>
<td>Mesangial cellularity: normal/increased</td>
</tr>
<tr>
<td>Podocytes: preserved or effaced (%), protein reabsorption granules, and microvillus change</td>
</tr>
<tr>
<td>Leukocytes/platelets/fibrin in capillary lumen/Bowman’s space</td>
</tr>
<tr>
<td>Tubular epithelial and basement membrane abnormalities when present</td>
</tr>
</tbody>
</table>
Some examples….Patient # 1

- Mr. GS is a 47-yr old man with proteinuria, hematuria and renal failure
- Serum creatinine 2.7 mg/dl, creatinine clearance 34 ml/min, urinary protein 2 gms/24 hours. Urinalysis- RBCs and few RBC casts
- History of hepatitis C, low complement titers
Subendothelial deposits

Double contour
Diagnosis

• **Primary diagnosis:** Immune-complex glomerulonephritis (hepatitis C/clinical)

• **Pattern of injury:** Membranoproliferative glomerulonephritis

• **Additional features:**
  - with features of cryoglobulinemic glomerulonephritis (hepatitis C/clinical),
  - focal (20%) global glomerulosclerosis, moderate (30%) tubular atrophy and interstitial fibrosis
  - moderate arteriosclerosis and moderate hyaline arteriolosclerosis
Patient #2

- 58-year old man with nephrotic syndrome, hypertension, hyperlipidemia and edema.
- Serum creatinine 1.6 mg/dL
- UA- 30-50 RBC/HPF, with RBC casts
- Urine IFE kappa light chains
Kidney Biopsy

A

B

C

D

E

F

IgG

C3

Kappa

Lambda

KDIGO
Diagnosis

- **Primary diagnosis:** Proliferative glomerulonephritis with monoclonal Ig deposits

- **Pattern of injury:** Membranoproliferative glomerulonephritis

- **Additional features:**
  - focal global glomerulosclerosis (30%), moderate (40%) tubular atrophy and interstitial fibrosis,
  - moderate arteriosclerosis and moderate hyaline arteriolosclerosis

**Ancillary study:** IgG subtyping reveals **IgG3 subclass**, negative for IgG1, IgG2 and IgG4
Patient # 3

- 61-year old man with monoclonal gammopathy (IgG kappa protein with M spikes ranging from 0.5 to 0.9 g/dL over time), low complement titers (low C3 normal C4), and gross hematuria, few RBC casts. Serum creatinine 1.3 mg/dL

- Bone marrow 8% plasma cells: MGUS

- Biopsied in 07 and 09
Double contours

Mesangial & Endocapillary proliferation
Negative IgG, IgM, IgA, C1q, kappa and lambda
Mesangial deposits

Capillary wall deposits: subendothelial and subepithelial deposits
Diagnosis

• **Primary diagnosis**: C3 glomerulonephritis

• **Pattern of injury**: Membranoproliferative glomerulonephritis

• **Additional features**:
  – Focal (20%) global glomerulosclerosis, mild (20%) tubular atrophy and interstitial fibrosis, mild arteriosclerosis and moderate hyaline arteriolosclerosis
Patient # 4

- A 68-year-old woman presents with acute renal failure, hematuria, proteinuria, and pulmonary infiltrates.
- Serum creatinine of 3.8 mg/dL. Hemoglobin is low at 5.8.
- The patient has positive MPO/pANCA and ANA titers. Remaining serological evaluation is negative.
- Urine analysis shows numerous red blood cells and few RBC casts.
Negative IF and EM studies
Kidney, needle biopsy:

**Primary diagnosis:** MPO-ANCA glomerulonephritis (MPO/clinical)

- **Pattern of injury:** necrotizing and crescentic glomerulonephritis
- **Prognostic class:** Focal (≥50% normal glomeruli)
- **Additional features:** Focal global glomerulosclerosis (10%), mild tubular atrophy and interstitial fibrosis (10%), mild arteriosclerosis and moderate hyaline arteriolosclerosis
Patient #5

- 63-year old woman with subacute rise in serum creatinine from 1.8 to 3.7 mg/dL over the last 3 weeks.
- UA- 2+ protein 3+ blood, 100-200 RBC/HPF
- PR3+ cANCA +
- Remaining serology negative
Negative IF and EM studies
Kidney, needle biopsy:

**Primary diagnosis:** PR3-ANCA glomerulonephritis (PR3/clinical)

- **Pattern of injury:** necrotizing and crescentic glomerulonephritis
- **Prognostic class:** Mixed (<50% normal glomeruli)
- **Additional features:** Severe ATN, Focal global glomerulosclerosis (33%), moderate tubular atrophy and interstitial fibrosis (30%), mild arteriosclerosis and moderate hyaline arteriolosclerosis
Other examples: IgA nephropathy

**Primary diagnosis**: IgA nephropathy

**Pattern of injury**: Mesangial proliferative and sclerosing glomerulonephritis

**Score/Grade**: Oxford classification: M1 E0 S1 T1

**Additional features**: Focal (20%) global glomerulosclerosis, moderate (30%) tubular atrophy and interstitial fibrosis, mild arteriosclerosis and severe hyaline arteriolosclerosis

**Secondary diagnoses**: Diabetic nephropathy, early
Lupus nephritis

- **Primary diagnosis**: Lupus nephritis

- **Pattern of injury**: Diffuse proliferative and sclerosing glomerulonephritis, with focal (10%) cellular crescents

- **Score/grade**: ISN/RPS class IV-G (A/C)

- **Additional features**:
  - Glomerular and arteriolar fibrin thrombi (anti-phospholipid antibodies/clínica)
  - Focal global glomerulosclerosis (20%), mild tubular atrophy and interstitial fibrosis (20%), moderate arteriosclerosis and moderate hyaline arteriolosclerosis
Anti-GBM glomerulonephritis

• **Primary diagnosis:** Anti-GBM glomerulonephritis

• **Pattern of injury:** Necrotizing and crescentic glomerulonephritis, severe

• **Additional features:**
  – Clinicopathologic features of Goodpasture syndrome (anti-GBM antibody/clinical),
  – focal global glomerulosclerosis (40%), moderate tubular atrophy and interstitial fibrosis (40%), mild arteriosclerosis and moderate hyaline arteriolosclerosis
The main aim and purpose of consensus meeting was to classify glomerulonephritis based on the underlying pathophysiology and etiology.

Based on the current knowledge there are five basic classes of GN:
- immune–complex GN
- pauci-immune GN
- anti-GBM GN
- monoclonal Ig GN
- C3 glomerulopathy

Specific entities exist within each group

The consensus document provides guidelines for the kidney biopsy report on glomerulonephritis
Shortcomings and limitations/needs further work

- Difficult cases - the diagnosis is not clear cut
- Limited biopsy sample
- Multiple diagnoses - GN + non GN diagnosis
- New disease entities
- Far from complete, work in progress, future modifications
Example

- A 72 year old woman with hypertension and diabetes presented with acute on chronic kidney disease.
- Serum creatinine up from baseline of 1.5 to 2.1 mg/dL
- UA shows 3+ blood and 2+ protein
- Tobacco use
Final Diagnosis

Kidney, needle biopsy:

Primary diagnosis: 1) Pauci-immune glomerulonephritis.
2) Diffuse and nodular diabetic glomerulosclerosis, moderately advanced.

Pattern of injury: 1) Necrotizing and crescentic glomerulonephritis. 2) Diffuse and nodular glomerulosclerosis.

Score: Mixed class.

Additional findings: Focal (27%) global glomerulosclerosis, moderate (30%) tubular atrophy and interstitial fibrosis, moderate arterial sclerosis.
Mayo Clinic/Renal Pathology Society Consensus Report on Pathologic Classification, Diagnosis, and Reporting of GN


*Mayo Clinic, Rochester, Minnesota

A Systematic Method for Categorizing GN

Richard J. Johnson,* Stuart J. Shankland,† and M. Scott Lucia‡

*Division of Renal Diseases and Hypertension and †Department of Pathology, University of Colorado Anschutz Medical Campus, Aurora, Colorado; and ‡Division of Nephrology, University of Washington, Seattle, Washington