Classification of Glomerular Diseases and Defining Individual Glomerular Lesions: Developing International Consensus

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Statement of Disclosure

Mark Haas serves as a paid consultant on pathology adjudication committees for two industry-sponsored clinical trials:

Shire ViroPharma – Treatment of Acute ABMR
AstraZeneca – Treatment of Proliferative Lupus Nephritis

He has also received honoraria from CareDx for serving as a symposium speaker

None represent a conflict of interest relevant to any of the material presented in this talk.
1. Classification and Reporting of GN: The 2015 Mayo Clinic/RPS Consensus
2. Standardized grading of chronic changes in native kidney biopsies
3. Development of consensus definitions for individual glomerular lesions
4. Development of consensus diagnostic criteria for complex disease processes – microangiopathic changes/thrombotic microangiopathy
5. Kidney Biopsy Codes Project (KBC)
Classification and Reporting of GN: The 2015 Mayo Clinic/RPS Consensus Meeting

2 Basic Goals

• Develop a basic classification of GN based primarily on etiology/pathophysiology, rather than morphologic pattern

• Develop a way to incorporate this into the pathology report:
  • Logical
  • Sequential
  • Reproducible
  • And most importantly addresses the key clinical questions
An Example

- 61-year old man with monoclonal gammopathy (IgG-kappa with M spikes ranging from 0.5 to 0.9 g/dL over time), low serum C3 with normal C4, microscopic and intermittent gross hematuria, few RBC casts.

- Serum creatinine 1.3 mg/dL

- Bone marrow 8% plasma cells: MGUS
Negative IgG, IgM, IgA, C1q, kappa and lambda
Mesangial deposits

Subendothelial and subepithelial deposits
Diagnosis

- **Primary disease**: C3 glomerulonephritis

- **Pattern of injury**: Mesangial and focal/segmental endocapillary proliferative GN

- **Additional features**:
  - Mild (10%) tubular atrophy and interstitial fibrosis
  - Underlying monoclonal gammopathy (clinical)
An example incorporating current morphologic classifications: IgA nephropathy

**Primary disease:** IgA nephropathy

**Pattern of injury:** Mesangial proliferative and segmental sclerosing glomerulonephritis with rare fibrocellular crescents

**Score/Grade:** Oxford classification: M1 E0 S1 T1 C1

**Additional features:** Focal (20%) global glomerulosclerosis, moderate (30%) interstitial fibrosis and tubular atrophy, mild arteriosclerosis and moderate hyaline arteriolar sclerosis
Another example incorporating current morphologic classifications: **lupus nephritis**

- **Primary disease:** Lupus nephritis

- **Pattern of injury:** Diffuse active (proliferative) and focal/segmental sclerosing glomerulonephritis, with focal (10%) cellular crescents and “wire loop” deposits

- **Score/grade:** Revised ISN/RPS class IV; NIH activity index 7/24, chronicity index 3/12

- **Additional features:**
  - Glomerular and arteriolar fibrin thrombi (history of anti-phospholipid antibodies - clinical)
  - Mild tubular atrophy and interstitial fibrosis (15%), moderate arteriosclerosis and mild hyaline arteriolosclerosis
The main aim and purpose of consensus meeting was to classify glomerulonephritis based on the underlying pathophysiology and etiology.

Based on current knowledge there are five basic classes of GN:

- immune–complex GN (incl. IgAN, PIGN, lupus, etc.)
- pauci-immune GN
- anti-GBM GN
- monoclonal Ig GN (incl. prolif. GN with monocl. IgG)
- C3 glomerulopathy (includes C3GN and DDD)

Specific entities exist within each group

The consensus document provides guidelines for the kidney biopsy report on glomerulonephritis
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 Luda‡

*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


doi: 10.1681/ASN.2015101160
A proposal for standardized grading of chronic changes in native kidney biopsy specimens

<table>
<thead>
<tr>
<th></th>
<th>Score= 0</th>
<th>Score= 1</th>
<th>Score= 2</th>
<th>Score= 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulosclerosis (GS score)</td>
<td>&lt;10%</td>
<td>10-25%</td>
<td>26-50%</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Interstitial fibrosis (IF score)</td>
<td>&lt;10%</td>
<td>10-25%</td>
<td>26-50%</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Tubular atrophy (TA score)</td>
<td>&lt;10%</td>
<td>10-25%</td>
<td>26-50%</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Arteriosclerosis (CV score)</td>
<td>&lt; thickness of media</td>
<td>≥ thickness of media</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Minimal chronic changes</td>
<td>0-1</td>
</tr>
<tr>
<td>Mild chronic changes</td>
<td>2-4</td>
</tr>
<tr>
<td>Moderate chronic changes</td>
<td>5-7</td>
</tr>
<tr>
<td>Severe chronic changes</td>
<td>&gt;7</td>
</tr>
</tbody>
</table>
Interstitial inflammation

Tubular atrophy

Interstitial fibrosis

Application of the Chronicity Score to A Pathologically Diverse Cohort of 676 Patients  
Srivastava et al, JASN 29: 2213-2224, 2018

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferative GN</td>
<td>30.2</td>
</tr>
<tr>
<td>Nonproliferative glomerulopathies</td>
<td>18.2</td>
</tr>
<tr>
<td>Advanced glomerulosclerosis</td>
<td>11.5</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>11.1</td>
</tr>
<tr>
<td>Vascular</td>
<td>8.0</td>
</tr>
<tr>
<td>Tubulointerstitial</td>
<td>7.3</td>
</tr>
<tr>
<td>Paraprotein</td>
<td>7.3</td>
</tr>
<tr>
<td>Other</td>
<td>6.5</td>
</tr>
</tbody>
</table>
Chronic histopathologic lesions are associated with ≥40% eGFR decline or ESRD

Anand Srivastava et al. JASN 2018;29:2213-2224
# Application of the Chronicity Score to A Pathologically Diverse Cohort of 676 Patients

Srivastava et al, JASN 29: 2213-2224, 2018

<table>
<thead>
<tr>
<th>Chronicity Score of Sethi et al</th>
<th>$N$</th>
<th>Events per 100 person-yr</th>
<th>Model 1 HR [95% CI]</th>
<th>Model 2 HR [95% CI]</th>
<th>Model 3 HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per one-point change</td>
<td>654</td>
<td>12.1</td>
<td>1.28 [1.22 - 1.33]</td>
<td>1.23 [1.17 - 1.30]</td>
<td>1.19 [1.12 - 1.27]</td>
</tr>
<tr>
<td>Minimal chronic changes (0–1)</td>
<td>199</td>
<td>3.6</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mild chronic changes (2–4)</td>
<td>168</td>
<td>8.1</td>
<td>2.02 [1.17 - 3.48]</td>
<td>1.72 [0.97 - 3.06]</td>
<td>1.53 [0.85 - 2.75]</td>
</tr>
<tr>
<td>Moderate chronic changes (5–7)</td>
<td>146</td>
<td>17.3</td>
<td>4.24 [2.55 - 7.04]</td>
<td>3.81 [2.20 - 6.59]</td>
<td>2.92 [1.61 - 5.31]</td>
</tr>
</tbody>
</table>

Model 1 = unadjusted; Model 2 = adjusted for age, sex, race, primary diagnosis, and RAS blockade; Model 3 = Model 2 + adjustment for baseline eGFR.
Is this a crescent?
Definition of a Cellular Crescent (2016)

**Oxford IgAN**
extracapillary hypercellularity of **>2 cell layers** and involving **>10%** of the capsular circumference, composed of **>50% cells**

**ISN/RPS (2003)**
extracapillary cell proliferation of **>2 cell layers**, occupying **>25%** the glomerular capsular circumference

**Neptune/INTEGRATE**
extracapillary cell proliferation of **>2 cell layers** with **>50%** of the lesion occupied by cells

**Cure GN**
**>10%** of Bowman’s space with **>2 layers** cells or fibrosis; composed of **>50% cells and <50% matrix**
Exclude collapsing FSGS
If we are going to include in biopsy reports grades of glomerular diseases based on individual histologic lesions (e.g., Oxford C score which is based on the fraction of glomeruli with cellular or fibrocellular crescents; lupus activity index which includes cellular/fibrocellular crescents), and perform clinico-pathologic correlative studies using these grading systems that are likely to influence how patients are treated, it would be helpful to have uniform definitions of the individual lesions that compose these classifications.
In response to this need for uniform definitions of individual lesions seen on renal biopsies, in 2016 the Renal Pathology Society (RPS) agreed to form a committee consisting of 13 RPS members from North America, Europe, and Asia (including members directly involved in developing currently used classifications) to develop a consensus set of definitions for individual glomerular lesions seen on examination of renal biopsies that can be applied across the varying disease classification schemes that currently exist, and can be applied to future disease classifications as well.
Committee Members (in alphabetical order)

Kerstin Amann
Ingeborg Bajema
Laura Barisoni
Jan Ulrich Becker
Zeng Cai
Mark Haas
Charles Jennette
Kensuke Joh
Danica Ljubanovic
Ian Roberts
Joris Roelofs
Surya Seshan
Sanjeev Sethi
At a meeting of the committee held in San Antonio, Texas in concert with the USCAP meeting in March 2017, a list of individual, light microscopic glomerular lesions to be defined was compiled. This list included 53 lesions subdivided into seven categories: mesangial (3), capillary (14), extracapillary (15), sclerosing and collapse (8), necrosis (2), glomerular size (3), and injury patterns (8).
From subsequent meetings, discussions, and exchanges, this list was reduced to 47 (including lesion subsets, such as cellular, fibrocellular, and fibrous crescents) by elimination of highly overlapping terms, and by April, 2018 the committee had agreed on consensus definitions for the 47 light microscopic lesions. A preliminary list of 54 definitions of structures, anatomic sites/locations, and abnormalities seen by EM has also been developed, and work has begun compiling the different published definitions for each of these, based on which consensus definitions will be developed.
### Definition of a Cellular Crescent

<table>
<thead>
<tr>
<th>Oxford IgAN</th>
<th>ISN/RPS (2003)</th>
<th>Neptune/INTEGRATE</th>
<th>Cure GN</th>
</tr>
</thead>
<tbody>
<tr>
<td>extracapillary hypercellularity of (&gt;2) cell layers and involving (&gt;10%) of the capsular circumference, composed of (&gt;50%) cells</td>
<td>extracapillary cell proliferation of (&gt;2) cell layers, occupying (&gt;25%) the glomerular capsular circumference</td>
<td>extracapillary cell proliferation of (&gt;2) cell layers with (&gt;50%) of the lesion occupied by cells</td>
<td>(&gt;10%) of Bowman’s space with (&gt;2) layers cells or fibrosis; composed of (&gt;50%) cells and (&lt;50%) matrix \nExclude collapsing FSGS</td>
</tr>
</tbody>
</table>

**Proposed ISN/RPS Revision (KI 93: 789-796, 2018)**

- change proliferation to hypercellularity
- change \(>25\%\) to \(>10\%\) to be in line with other classifications, but also changed \(>50\%\) of the lesion occupied by cells to \(>75\%\) of the lesion occupied by cells or fibrin and \(<25\%\) occupied by fibrous matrix

The committee chose to adopt the revised ISN/RPS revised definition, above
Another Example of a Consensus LM Definition – fibrinoid necrosis

<table>
<thead>
<tr>
<th>Oxford IgAN and Neptune/Integrate</th>
<th>ISN/RPS (2003)</th>
<th>Cure GN</th>
<th>Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>fibrin exudation associated with GBM rupture and/or lysis of the mesangial matrix</td>
<td>disruption of the GBM with fibrin exudation and karyorrhexis</td>
<td>fibrin in zones of necrosis with breaks in GBMs and/or lysis of mesangial matrix</td>
<td>fibrin associated with GBM disruption and/or lysis of the mesangial matrix</td>
</tr>
</tbody>
</table>

While this may not seem like a big deal, fibrinoid necrosis is a key component of the NIH Activity Index (AI) for lupus nephritis. The elimination of karyorrhexis from the definition has important implications as the proposed update for the ISN/RPS classification (Bajema et al, KI 93: 789-796, 2018) recommends using an updated version of the AI including the consensus definition above.
A key limitation of our committee’s approach, however, is that it is limited to individual lesions and does not address disease processes composed of >1 potential lesion. In addition, our current definitions are limited to glomerular lesions and do not address related or unrelated tubulo-interstitial or vascular lesions.

An example of a disease process often composed of >1 lesion and often involving >1 compartment is thrombotic microangiopathy (TMA), or more broadly microangiopathic change, since actual thrombosis is not always evident.
Lack of a consensus definition for microangiopathy is a problem! Example – IgA nephropathy

<table>
<thead>
<tr>
<th>Study/Location</th>
<th># IgAN Pts</th>
<th>#/% w/ MA change</th>
<th>Diag. Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang et al (2006)</td>
<td>435</td>
<td><strong>10 (2.3%)</strong></td>
<td>LM, EM</td>
</tr>
<tr>
<td>Seattle, USA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>El-Karoui et al (2012)</td>
<td>128</td>
<td><strong>68 (53%)</strong></td>
<td>LM, IHC (CD61, 12 cases)</td>
</tr>
<tr>
<td>Paris, France</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beijing, China</td>
<td></td>
<td></td>
<td>(EM - 194 cases)</td>
</tr>
<tr>
<td>Haas et al (2018)</td>
<td>2290</td>
<td><strong>49 (2.2%)</strong></td>
<td>LM, EM</td>
</tr>
<tr>
<td>Los Angeles, USA</td>
<td></td>
<td></td>
<td>(EM on 85%)</td>
</tr>
</tbody>
</table>
Kidney Biopsy Codes (KBC) Project

**Goal**
To harmonize kidney biopsy registration, proposing unified and well-structured codes and terms everyone can use

**Project Leaders**
- Amélie Dendooven
- Mark Helbert
- Sabine Leh
Kidney Biopsy Registries
How do registries code?

**POLISH REGISTRY OF RENAL BIOPSIES (PRRB)**
124 Class IV (diffuse proliferative) lesions in IgA nephropathy

**SPANISH REGISTRY OF GLOMERULONEPHRITIS**
? IgA nephropathy

**CZECH REGISTRY OF RENAL BIOPSIES (CRRB)**
1730 IgA nephropathy with crescents

**PATOBANK (DENMARK)**
T 71000 kidney
M46862 diffuse mesangial proliferative GN
S67300 IgA nephritis
M53300 glomerulosclerosis
M58000 tubular atrophy

**JAPAN RENAL BIOPSY REGISTRY (J-RBR)**
IgA nephropathy (histological diagnosis by pathogenesis)
Mesangial proliferative glomerulonephritis (histological diagnosis by histopathology)

**FLEMISH COLLABORATIVE GLOMERULONEPHRITIS GROUP (FCGG-NBVN)**
FCGG-NBVN 3/3a IgA nephropathy / IgA nephropathy, primary
ERA-EDTA PRD 1128 IgA nephropathy – histologically proven

**NORWEGIAN RENAL REGISTRY (NNR)**
ERA-EDTA PRD 1128 IgA nephropathy – histologically proven
NNR 2013 300 IgA nefropati
NNR 2011 3 IgA nefropati

**SCOTTISH RENAL BIOPSY REGISTRY**
ERA-EDTA PRD 1128 IgA nephropathy – histologically proven

**ITALIAN REGISTRY OF RENAL BIOPSIES (IRRB)**
ERA-EDTA PRD 1128 IgA nephropathy – histologically proven

**BRITISH COLUMBIA GLOMERULONEPHRITIS NETWORK**
G23.1 IgA nephropathy primary
V3 Hypertensive/benign/ischemic nephrosclerosis

**Oxford classification:** M1 E0 S1 T0 C1

**IgA nephropathy**
Mesangial proliferative GN
15 glomeruli, 1 cellular crescent, 2 segmental sclerosis, 4 global glomerulosclerosis.
Tubular atrophy in ~20% of the cortical area. Moderate arteriolosclerosis and arteriosclerosis.
IH: Dominant IgA positivity
EM: Mesangial electron dense deposits

**NNR 2013**
300 IgA nefropati

**NNR 2011**
3 IgA nefropati

**FLEMISH COLLABORATIVE GLOMERULONEPHRITIS GROUP (FCGG-NBVN)**
FCGG-NBVN 3/3a IgA nephropathy / IgA nephropathy, primary
ERA-EDTA PRD 1128 IgA nephropathy – histologically proven
Thank you for your attention. Any questions?