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

Neither represents a conflict of interest relevant to any of the material presented in this talk.
Brief summary of currently used glomerular disease classifications

- Similarities/differences in derivation, approach
- The Oxford/MEST classification of IgA nephropathy: the evidence-based standard
  - Update to include crescents
- “Expert opinion-based” classifications: the ISN/RPS lupus nephritis classification
  - Improving this and other opinion-based classifications
- Mayo Clinic/RPS proposals for standardization of reporting of GN and grading of chronic changes
- Ongoing international efforts to standardize definitions of individual glomerular lesions across different classifications
Currently Utilized Morphologic Classification Schemes for Glomerular Diseases

IgA Nephropathy – Oxford (MEST) Classification
Catran et al, Kidney Int 76: 534-545, 2009

ISN/RPS Classification of Lupus Nephritis
Weening et al, Kidney Int 65: 521-530, 2004

Columbia Classification of FSGS

Classification of ANCA-GN (Leiden)

Classification of Diabetic Nephropathy (Leiden)
These Classifications Differ in How They Were Derived

Oxford Classification of IgA Nephropathy
Evidence-based derivation based on reproducibility between pathologists and correlation with clinical outcomes (slope of eGFR decline, composite endpoint of ESRD/≥50% decline in eGFR) - Took 5 years to develop

ISN/RPS Classification of Lupus Nephritis
Consensus of expert opinion, based on existing literature and experience with previous iterations of the WHO classification

Columbia Classification of FSGS
Consensus of expert opinion, based on existing literature

Classifications of ANCA-GN and Diabetic Nephropathy
Consensus of expert opinion, based on existing literature and single-center clinico-pathologic studies
The Classifications Also Differ in Their Approach

The Oxford Classification is not a grading system per se, but rather assesses five morphologic parameters shown to correlate with clinical outcomes and/or response to therapy, using evidence-based cutoffs for these parameters (M, E, S, T, C). However, with regard to clinical correlation Oxford has generally proved superior to previous classifications of IgA nephropathy based on specific classes or grades (e.g., Lee and Haas).

By contrast, each of the other classifications divide lesions into specific histologic subtypes (Columbia FSGS, ANCA-GN), or numbered classes and subclasses (ISN/RPS, Diabetic Nephropathy).
### Multivariate Determinants of Survival from ESRD or ≥50% Decline in eGFR (2394 patients)

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>No Immunosuppression</th>
<th>Any Immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>p</td>
</tr>
<tr>
<td>eGFR at biopsy</td>
<td>0.99</td>
<td>0.98-0.99</td>
<td>&lt;0.001</td>
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<tr>
<td>TA MAP (mmHg)</td>
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<td>TA Proteinuria (g/day)</td>
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<td>1.51-1.68</td>
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</tr>
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<td>M (1 versus 0)</td>
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<td>1.11-1.70</td>
<td>0.003</td>
</tr>
<tr>
<td>E (1 versus 0)</td>
<td>0.76</td>
<td>0.56-1.04</td>
<td>0.08</td>
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<tr>
<td>S (1 versus 0)</td>
<td>1.45</td>
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<td>T (1-2 versus 0)</td>
<td>2.85</td>
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<td>1.07-1.75</td>
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Haas, Verhave, ............, Troyanov, Katafuchi, JASN 28: 691-701, 2017
Any vs no crescent

No (reference), <1/6, ≥ 1/6
gglomeruli with crescents

No (reference), <1/4, ≥ 1/4
gglomeruli with crescents

Adjusted hazard ratio of a combined event

Haas, Verhave, …………., Troyanov, Katafuchi, JASN 28: 691-701, 2017
A crescent (C) score was thus added to the Oxford MEST score (MEST-C):

**C0** – no crescents (cellular or fibrocellular)

**C1** – crescents in <25% of glomeruli
   identifies patients at risk of poor outcome if not given immunosuppressive therapy

**C2** – crescents in ≥25% of glomeruli
   identifies patients at risk of poor outcome even if given immunosuppressive therapy
ISN/RPS Classification of Lupus Nephritis (2004)

Class I  Minimal mesangial lupus nephritis
  Normal glomeruli by LM, mesangial immune deposits by IF

Class II  Mesangial proliferative lupus nephritis
  Purely mesangial hypercellularity or matrix expansion by LM with
  mesangial immune deposits (may be few subendothelial and/or
  subepithelial deposits by IF or EM, but not by LM)

Class III  Focal lupus nephritis (segmental and/or global, active and/or
  sclerosing, endocapillary and/or extracapillary GN involving <50% of
  glomeruli, with or without mesangial alterations)
  (A)  Purely active lesions; focal proliferative
  (A/C)  Active and chronic lesions; focal proliferative and sclerosing
  (C)  Chronic inactive; focal sclerosing
ISN/RPS Classification (2004), continued

Class IV  Diffuse lupus nephritis (segmental and/or global, active and/or sclerosing, endocapillary and/or extracapillary GN involving >50% of glomeruli, with or without mesangial alterations)
Class IV is further divided into diffuse segmental (IV-S) when >50% of involved glomeruli have segmental lesions (involving less than half of the glomerular tuft) and diffuse global (IV-G) when >50% of involved glomeruli have global lesions (involving at least half of the tuft)
(A) Purely active lesions; diffuse segmental [IV-S (A)] or diffuse global [IV-G (A)] proliferative
(A/C) Active and chronic lesions; diffuse segmental [IV-S (A/C)] or diffuse global [IV-G (A/C)] proliferative and sclerosing
(C) Chronic inactive; diffuse segmental [IV-S (C)] or diffuse global [IV-G (C)] sclerosing

Class V  Membranous lupus nephritis (with or without mesangial alterations)

Class VI  Advanced sclerosing lupus nephritis (>90% globally sclerotic without residual activity)
Kappa values

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<tr>
<th>Category</th>
<th>Value</th>
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<td>ISN/RPS Class</td>
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<td>WHO 1995 Class</td>
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</tr>
<tr>
<td>ISN/RPS IV-G vs IV-S</td>
<td>0.35</td>
</tr>
<tr>
<td>ISN/RPS (A) vs (A/C) vs (C)</td>
<td>0.33</td>
</tr>
</tbody>
</table>
Plan for Resolution of the IV-G/IV-S Issue (I. Bajema et al, Leiden)

**Level 1:** Recommend abandoning the segmental/global subdivision within Class IV as specified in ISN/RPS classification.

**Level 2:** Evaluate the clinical significance of glomerular necrotizing lesions, defined as fibrin associated with GBM disruption and/or lysis of the mesangial matrix, with or without karyorrhexis. Incorporate such lesions into a revised classification if so indicated by the data.
The Designations of A, A/C, and C within Classes III and IV are not very helpful (or reproducible)

The great majority of Class III and IV lesions are A/C
A biopsy with multiple necrotizing and crescentic lesions and 15% IFTA will be graded A/C, as will a biopsy with 60% IFTA and a single glomerulus with endocapillary hypercellularity and/or a cellular crescent

Level 1 recommendation: Replace A, A/C, and C with a modified version of the more granular NIH activity and chronicity indices
Level 2: Establish evidence-based cutoffs and weighting for the different components of AI and CI
# Activity & Chronicity Indices in Lupus Nephritis

**Activity Index (each 0–3; max 24)**  

- Glomerular cell proliferation
- Cellular crescents 2x
- Fibrinoid necrosis/karyorrhexis 2x
- “Wire loops”, hyaline thrombi
- Glomerular leukocyte infiltration
- Interstitial mononuclear cell infiltration

**Chronicity Index (each 0–3; max 12)**

- Glomerular sclerosis
- Fibrous crescents
- Interstitial fibrosis
- Tubular atrophy

**Modified Activity Index (each 0-3; max 24)**

- Endocapillary hypercellularity
- Cellular/fibrocellular crescents 2x
- Fibrinoid necrosis 2x
- Hyaline deposits (“WL”, hyal. thrombi)
- Glomerular neutrophils, karyorrhexis
- Interstitial Inflammation

**Modified Chronicity Index (each 0-3; max 12)**

- Glomerular sclerosis (glob + segm)
- Fibrous crescents
- Interstitial fibrosis
- Tubular atrophy

For modified indices: 0 - none; 1 - <25%; 2 - 25-50%; 3 - >50%
The ISN/RPS Classes are based entirely on glomerular lesions, and do not consider tubulo-interstitial or vascular lesions.

However, in a number of different glomerular diseases (e.g., IgA nephropathy), it is well documented that one of if not the strongest predictor of poor clinical outcomes (e.g., ESRD, 50% reduction in eGFR, doubling of SCr, rate of eGFR decline) is the extent of interstitial fibrosis and tubular atrophy (IFTA).
Interstitial inflammation

Tubular atrophy

Interstitial fibrosis

Yu et al, Kidney Int 77: 820-829, 2010
Activity and chronicity indices **DO** include interstitial fibrosis (CI), tubular atrophy (CI), and interstitial inflammation (AI); **level 2** studies will evaluate cutoffs, whether IF and TA should be considered separately or together, and whether inflammation in areas of IF/TA should be considered in the AI.

The prognostic impact of vascular lesions including TMA, lupus vasculopathy (vascular IC deposits without associated inflammation), and vasculitis will be evaluated in **level 2**.
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
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
- 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.
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

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

<table>
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<tr>
<th></th>
<th>Score= 0</th>
<th>Score= 1</th>
<th>Score= 2</th>
<th>Score= 3</th>
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<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>
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<td></td>
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<tr>
<td>Minimal chronic changes</td>
<td>0-1</td>
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<td></td>
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<tr>
<td>Mild chronic changes</td>
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</tr>
<tr>
<td>Moderate chronic changes</td>
<td>5-7</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Severe chronic changes</td>
<td>&gt;7</td>
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</table>
Interstitial inflammation

Tubular atrophy

Interstitial fibrosis

Yu et al, Kidney Int 77: 820-829, 2010
Is this a crescent?
### Definition of a Cellular Crescent

<table>
<thead>
<tr>
<th>Oxford IgAN</th>
<th>ISN/RPS</th>
<th>Neptune/INTEGRATE</th>
<th>Cure GN</th>
</tr>
</thead>
<tbody>
<tr>
<td>extracapillary hypercellularity of $\geq 2$ cell layers and involving $&gt;10%$ of the capsular circumference, composed of $&gt;50%$ cells and fibrin, and $&lt;50%$ fibrous matrix</td>
<td>extracapillary cell proliferation of $\geq 2$ cell layers, with $\geq 50%$ of the lesion occupied by cells and involving $&gt;25%$ of the circumference of Bowman’s capsule</td>
<td>extracapillary cell proliferation of $\geq 2$ cell layers with $&gt;50%$ of the lesion occupied by cells and $&lt;50%$ by matrix</td>
<td>$&gt;10%$ of Bowman’s space with $&gt;2$ layers cells or fibrosis; composed of $\geq 50%$ cells and $&lt;50%$ matrix</td>
</tr>
</tbody>
</table>
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 12 RPS members from North America, Europe, and Asia to develop a consensus set of definitions for individual glomerular lesions seen on histologic 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.
At a meeting of the committee held in San Antonio, Texas in concert with the USCAP meeting in March 2017, a list of individual glomerular lesions to be defined was compiled. This list includes 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).
How can we improve on current classifications that are based on expert opinion?

A 2-step approach:

1. **Modify definitions** of and cutoffs/thresholds for specific lesions where there are inconsistencies, vagueness, and omissions; use examples to clarify details and illustrate difficult issues

2. **Evidence-based, multicenter study** involving scoring of parameters and relation to clinical outcome(s), using results to guide modification of the existing classification
Thank you for your attention. Any questions?