## Classification of Lupus Glomerulonephritis: Five Years Later

**J. Charles Jennette, MD**

<table>
<thead>
<tr>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV-G</th>
<th>Class IV-S</th>
<th>Class V</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>
Who Classified Lupus Nephritis?

“Original WHO Classification”
Buffalo, NY, 1974; or Geneva, 1975

“Modified WHO Classification”
ISKDC, Paris, 1980 (Churg and Sobin, 1982)

“Modified WHO Classification”
Churg 1995
Class I. Normal
  Normal by LM, EM and IF

Class II. Mesangial Changes
  A. Minimal alterations
     (normal by LM, mesangial deposits by IF and EM)
  B. Mesangial Glomerulitis (mesangial hypercellularity)

Class III. Focal and Segmental Proliferative Glomerulonephritis
  (<50% glomeruli involved)

Class IV. Diffuse Proliferative Glomerulonephritis
  (>50% glomeruli involved)

Class V. Membranous Glomerulonephritis
  Pure
  Mixed Patterns (such as Class III associated with Class V)
Post card sent from Ed Lewis to Mel Schwrtz while Ed Lewis was at the 1980 ISKDC Meeting
I. Normal
   a. Nil (by all techniques)
   b. Normal by LM, but deposits by EM or IF
II. Pure Mesangial Alterations (Mesangiopathy)
   a. Mesangial widening/mild hypercellularity
   b. Moderate hypercellularity
III. Focal Segmental Glomerulonephritis
   a. Active necrotizing lesions
   b. Active and sclerosing lesions
   c. Sclerosing lesions
IV. Diffuse Glomerulonephritis
   a. Without segmental lesions
   b. Without segmental lesions
   c. Without segmental lesions
   d. Like a., b. and c. above
V. Diffuse Membranous Glomerulonephritis
   a. Pure
   b. Associated with category II
   c. Associated with category III
   d. Associated with category IV
VI. Advanced Sclerosing Glomerulonephritis
Jacob Churg, 1995: WHO Morphologic Classification of Lupus Nephritis (modified)

I. Normal
   A. Nil (by all techniques)
   B. Normal by LM, but deposits by EM or IF

II. Pure Mesangial Alterations (Mesangiopathy)
   A. Mesangial widening/mild hypercellularity
   B. Moderate hypercellularity

III. Focal Segmental Glomerulonephritis
   A. Active necrotizing lesions
   B. Active and sclerosing lesions
   C. Sclerosing lesions

IV. Diffuse Glomerulonephritis
   A. Without segmental lesions
   B., C., and D. like A., B. and C. above

V. Diffuse Membranous Glomerulonephritis
   A. Pure
   B. Associated with category II

VI. Advanced Sclerosing Glomerulonephritis

50% cutoff between III and IV
V-C and V-D deleted.
Problems with the WHO Lupus Nephritis Classification

- Different versions with no official peer-reviewed version
- Lack of precise definitions of terms and criteria for different classes
- Never validated for reproducibility
- Unnecessary subcategorization based on mesangial hypercellularity
- No guidance for classifying borderline lesions
- Confusion about class III and class IV
- Uncertainty about how to classify segmental necrotizing lesions
- Different approaches to classifying mixed proliferative and membranous lesions
- Cumbersome designations for activity and chronicity
Outcome of Lupus Nephritis

WHO Class IV

"WHO Class III (>50%)"

WHO Class” Vc (>50%)” & Vd

Outcome of Lupus Nephritis

Most renal pathologists would classify all of these as class IV

WHO Class IV

“WHO Class III (>50%)”

WHO Class” Vc (>50%)” & Vd

ISN/RPS Working Group on the Classification of Lupus Glomerulonephritis

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The Classification of Glomerulonephritis in Systemic Lupus Erythematosus Revisited


2004 ISN/RPS Consensus Conference on the Classification of Lupus Glomerulonephritis

Class I  Minimal mesangial lupus glomerulonephritis (LGN)
Class II Mesangial proliferative LGN
Class III Focal LGN (involving < 50% of glomeruli)
Class IV Diffuse LGN (involving 50% or > glomeruli)
   Class IVS Predominantly segmental
   Class IVG Predominantly global
Class V  Membranous LGN
Class VI Advanced sclerotic LGN (> 90% sclerotic glomeruli)
ISN/RPS Classification of Lupus Glomerulonephritis

Class I

Class II

Class III

Class IV-G

Class IV-S

Class V
ISN/RPS Classification of Lupus Glomerulonephritis

**Class I Minimal mesangial lupus glomerulonephritis.** Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence.
ISN/RPS Classification of Lupus Glomerulonephritis

**Class II Mesangial proliferative lupus glomerulonephritis.** Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits.

There may be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy.
ISN/RPS Classification of Lupus Glomerulonephritis

Class III Focal lupus glomerulonephritis. Active or inactive focal, segmental or
global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli,
typically with focal subendothelial immune deposits, with or without mesangial
(A/C): Active and chronic lesions: focal proliferative and sclerosing lupus nephritis.
Class III (C): Chronic inactive lesions with glomerular scars: focal sclerosing lupus
nephritis.
Class IV Diffuse lupus glomerulonephritis. Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving 50% or more of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when 50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when 50% of the involved glomeruli have global lesions. IV-S and IV-G are divided into (A): active lesions, (A/C): active and chronic lesions, and (C): chronic inactive lesions with scars.
ISN/RPS Classification of Lupus Glomerulonephritis

Class V Membranous lupus glomerulonephritis. Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations.

A diagnosis of both Class III & Class V or Class IV & Class V is given when there are combined lesions.
ISN/RPS Classification of Lupus Glomerulonephritis

Class VI Advanced sclerosis lupus glomerulonephritis. 90% or more of glomeruli globally sclerosed without residual activity. (ISN/RPS 2004)
<table>
<thead>
<tr>
<th>Lesion Description</th>
<th>Appel et al. 78</th>
<th>Churg 82</th>
<th>ISN/RPS 04</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lesion by LM, IF or EM</td>
<td>Class I</td>
<td>Class I A</td>
<td>No lupus GN</td>
</tr>
<tr>
<td>Mesangial deposits but no hypercellularity</td>
<td>Class II A</td>
<td>Class I B</td>
<td>Class I</td>
</tr>
<tr>
<td>Mesangial hypercellularity</td>
<td>Class II B</td>
<td>Class II A,B</td>
<td>Class II</td>
</tr>
<tr>
<td>Focal (&lt;50%) proliferative GN</td>
<td>Class III</td>
<td>Class III A,B,C</td>
<td>Class III A,A/C,C</td>
</tr>
<tr>
<td>Segmental (&gt;50%) GN</td>
<td>Class IV</td>
<td>Class IV B,C,D</td>
<td>Class IVS A,A/C,C</td>
</tr>
<tr>
<td>Diffuse (&gt;50%) Proliferative GN</td>
<td>Class IV</td>
<td>Class IV A,B,C,D</td>
<td>Class IVG A,A/C,C</td>
</tr>
<tr>
<td>Membranous</td>
<td>Class V</td>
<td>Class V</td>
<td>Class V</td>
</tr>
<tr>
<td>Membranous plus Proliferative</td>
<td>Class V&amp;III</td>
<td>Class VC</td>
<td>Class III&amp;V</td>
</tr>
<tr>
<td></td>
<td>Class V&amp;IV</td>
<td>Class VD</td>
<td>Class IV&amp;V</td>
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### Presenting clinical Manifestations of Different ISN/RPS Classes

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV-G</th>
<th>IV-S</th>
<th>V</th>
<th>VI</th>
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<tbody>
<tr>
<td></td>
<td>n=5</td>
<td>n=54</td>
<td>n=107</td>
<td>n=111</td>
<td>n=87</td>
<td>n=159</td>
<td>n=18</td>
</tr>
<tr>
<td>Asymptomatic hematuria</td>
<td>40</td>
<td>19</td>
<td>22</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Asymptomatic proteinuria</td>
<td>40</td>
<td>42</td>
<td>25</td>
<td>7</td>
<td>6</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>20</td>
<td>15</td>
<td>17</td>
<td>40</td>
<td>38</td>
<td>65</td>
<td>11</td>
</tr>
<tr>
<td>Nephritic syndrome</td>
<td>0</td>
<td>20</td>
<td>34</td>
<td>27</td>
<td>26</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>18</td>
<td>16</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>8</td>
<td>8</td>
<td>89</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

## Comparison of ISN/RPS Class IV Segmental (S) and Global (G) Variants

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># of patients</strong></td>
<td>24 S 35 G</td>
<td>11 S 22G</td>
<td>6 S 17 G</td>
<td>15 S 31G</td>
<td>22 S 22 Q 39 G</td>
<td>12 S 30G</td>
<td>14 S 41G</td>
</tr>
<tr>
<td><strong>S Cr</strong></td>
<td>S &gt; G</td>
<td>G &gt; S</td>
<td>G = S</td>
<td>G &gt; S</td>
<td>G=Q=S</td>
<td>G = S</td>
<td>G = S</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td>G &gt; S</td>
<td>G &gt; S</td>
<td>G = S</td>
<td>G &gt; S</td>
<td>G=Q=S</td>
<td>G &gt; S</td>
<td>G &gt; S</td>
</tr>
<tr>
<td><strong>HTN</strong></td>
<td>G &gt; S</td>
<td>G &gt; S</td>
<td>NR</td>
<td>G &gt; S</td>
<td>G=Q=S</td>
<td>G = S</td>
<td>G = S</td>
</tr>
<tr>
<td><strong>Wireloops</strong></td>
<td>G &gt; S</td>
<td>G &gt; S</td>
<td>NR</td>
<td>G &gt; S</td>
<td>G&gt;Q&gt;S</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td><strong>Focal necrosis</strong></td>
<td>S &gt; G</td>
<td>S &gt; G</td>
<td>NR</td>
<td>S &gt; G</td>
<td>G&gt;Q&gt;S</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td><strong>Cellularity</strong></td>
<td>G &gt; S</td>
<td>G &gt; S</td>
<td>NR</td>
<td>G &gt; S</td>
<td>NR</td>
<td>G &gt; S</td>
<td></td>
</tr>
<tr>
<td><strong>Ac index</strong></td>
<td>G = S</td>
<td>G = S</td>
<td>G &gt; S</td>
<td>G &gt; S</td>
<td>G=Q&gt;S</td>
<td>G = S</td>
<td>G = S</td>
</tr>
<tr>
<td><strong>Chr index</strong></td>
<td>S &gt; G</td>
<td>G = S</td>
<td>G &gt; S</td>
<td>G &gt; S</td>
<td>Q&gt;S&gt;G</td>
<td>G = S</td>
<td>G = S</td>
</tr>
<tr>
<td><strong>Worse outcome</strong></td>
<td>S &gt; G</td>
<td>G = S</td>
<td>S &gt; G Trend</td>
<td>G &gt; S</td>
<td>Q&gt;S&gt;G</td>
<td>G &gt; S</td>
<td>G &gt; S Trend</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>10yrs</td>
<td>55-38mth</td>
<td>95-214 mth</td>
<td>10yrs</td>
<td>10yrs</td>
<td>10yrs</td>
<td>10yrs</td>
</tr>
</tbody>
</table>
Lupus Sever Segmental Glomerulonephritis (SSGN, similar but not identical to IV-S) versus Lupus Diffuse Proliferatic Glomerulonephritis (DPGN, similar but not identical to IV-G)

Number (%) of renal biopsy specimens with the histologic finding:

<table>
<thead>
<tr>
<th></th>
<th>SSGN</th>
<th>←P→</th>
<th>DPGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>26</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Active lesions</td>
<td>26</td>
<td>0.9</td>
<td>15</td>
</tr>
<tr>
<td>Karyorrhexis</td>
<td>20 (78%)</td>
<td>0.7</td>
<td>13 (87%)</td>
</tr>
<tr>
<td>Fibrinoid necrosis</td>
<td>10 (38%)</td>
<td>0.3</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Capillary wall disruption</td>
<td>24 (92%)</td>
<td>0.04</td>
<td>8/13 (62%)</td>
</tr>
<tr>
<td>Crescents</td>
<td>13 (50%)</td>
<td>0.8</td>
<td>9 (60%)</td>
</tr>
<tr>
<td>Wire loops</td>
<td>9 (35%)</td>
<td>0.06</td>
<td>10 (67%)</td>
</tr>
<tr>
<td>Hyaline thrombi</td>
<td>3 (12%)</td>
<td>0.008</td>
<td>8 (53%)</td>
</tr>
</tbody>
</table>

### Lupus Sever Segmental Glomerulonephritis (SSGN, similar but not identical to IV-S) versus Lupus Diffuse Proliferative Glomerulonephritis (DPGN, similar but not identical to IV-G)

### Percent of glomeruli per of renal biopsy with the histologic finding:

<table>
<thead>
<tr>
<th></th>
<th>SSGN</th>
<th>DPGN</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>26</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Viable gloms/biopsy</td>
<td>19 ± 11</td>
<td>21 ± 11</td>
<td>0.5</td>
</tr>
<tr>
<td>Active lesions</td>
<td>80 ± 15%</td>
<td>98 ± 3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Karyorrhexis</td>
<td>19 ± 14%</td>
<td>18 ± 15%</td>
<td>0.7</td>
</tr>
<tr>
<td>Fibrinoid necrosis</td>
<td>6 ± 11%</td>
<td>4 ± 12%</td>
<td>0.3</td>
</tr>
<tr>
<td>Capillary wall disruption</td>
<td>23 ± 18%</td>
<td>17 ± 25%</td>
<td>0.1</td>
</tr>
<tr>
<td>Crescents</td>
<td>9 ± 13%</td>
<td>13 ± 20%</td>
<td>0.6</td>
</tr>
<tr>
<td>Wire loops</td>
<td>3 ± 6%</td>
<td>35 ± 34%</td>
<td>0.005</td>
</tr>
<tr>
<td>Hyaline thrombi</td>
<td>0.8 ± 3%</td>
<td>16 ± 22%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Lupus Sever Segmental Glomerulonephritis (SSGN, similar but not identical to IV-S) versus Lupus Diffuse Proliferative Glomerulonephritis (DPGN, similar but not identical to IV-G)

ISN/RPS IV-S and IV-G does not result in the same classification as Lewis-WHO III ≥ 50% and Lewis-WHO IV

Fig. 7. Renal survival comparing outcome in patients with severe lupus GN. A. Patients classified by the ISN/RPS classification. There is no difference in outcome between patients with diffuse segmental (IV-S) and diffuse global GN (IV-G), $P = 0.97$. B. The same patients classified by the WHO classification. The renal survival was significantly worse for patients with severe segmental GN (WHO class III ≥ 50%) than for patients with WHO class IV (WHO-IV), $P = 0.0028$.

ISN/RPS IV-S and IV-G does not result in the same classification as Lewis-WHO III ≥ 50% and Lewis-WHO IV

Crescents are a marker of an aggressive variant of lupus GN including the Lewis-WHO III ≥ 50%

Crescents are a marker of an aggressive variant of lupus GN including but not limited to the Lewis-WHO III ≥ 50%.

Schwartz et al “propose that diffuse global lupus GN with crescents is best described as WHO class IV + WHO class III.”

Five Years Later:

• The ISN/RPS Classification System has garnered widespread acceptance and use.

• The ISN/RPS Classification System has resulted in a higher level of interobserver reproducibility.

• Multiple studies have found that lupus nephritis ISN/RPS Class IV-S has similar or better outcomes than lupus nephritis ISN/RPS Class IV-G.

• Schwartz et al conclude that ISN/RPS class IV-S versus IV-G does not capture the major differences in prognosis and pathogenesis of severe lupus GN, and thus another round of classification adjustments is likely.
Anyone **WHO ISN’t** confused really doesn’t understand the situation.

Edward R. Murrow