Mayo Clinic/Renal Pathology Society Consensus Report on Pathologic Classification, Diagnosis, and Reporting of GN


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ABSTRACT
Renal pathologists and nephrologists met on February 20, 2015 to establish an etiology/pathogenesis-based system for classification and diagnosis of GN, with a major aim of standardizing the kidney biopsy report of GN. On the basis of etiology/pathogenesis, GN is classified into the following five pathogenic types, each with specific disease entities: immune-complex GN, pauci-immune GN, antiglomerular basement membrane GN, monoclonal Ig GN, and C3 glomerulopathy. The pathogenesis-based classification forms the basis of the kidney biopsy report. To standardize the report, the diagnosis consists of a primary diagnosis and a secondary diagnosis. The primary diagnosis should include the disease entity/pathogenic type (if disease entity is not known) followed in order by pattern of injury (mixed patterns may be present); score/grade/class for disease entities, such as IgA nephropathy, lupus nephritis, and ANCA GN; and additional features as detailed herein. A pattern diagnosis as the sole primary diagnosis is not recommended. Secondary diagnoses should be reported separately and include coexisting lesions that do not form the primary diagnosis. Guidelines for the report format, light microscopy, immunofluorescence microscopy, electron microscopy, and ancillary studies are also provided. In summary, this consensus report emphasizes a pathogenesis-based classification of GN and provides guidelines for the standardized reporting of GN.


A group of renal pathologists and nephrologists met at the Mayo Clinic (Rochester, MN) on February 20, 2015 to reach a consensus on the standardized classification and reporting of GN. The meeting was organized by S.S. and F.C.F. of the Mayo Clinic, endorsed by the Renal Pathology Society, and funded by an independent educational grant from the Fulk Foundation. The meeting opened with the identification of a major need for standardization of kidney pathology reporting in GN. Currently, the classification and reporting of GN are not standardized, which is disadvantageous for patient care, limits the ability to compare data between institutions, and hampers multicenter clinical and basic research. The focal point of the meeting was to recommend an etiology/pathogenesis-based classification of GN and standardize pathology reporting of GN. This manuscript describes the recommendations resulting from this meeting. The manuscript does not extend to other forms of glomerular diseases, such as membranous nephropathy, podocytopathies, and thrombotic microangiopathy.

GUIDELINES ON CLASSIFICATION OF GN

GN includes diseases characterized by increased glomerular cellularity caused by proliferation of indigenous cells and/or leukocyte infiltration. On the basis of pathogenesis/pathogenic type, there are five classes of GN: immune-complex GN,
pauci-immune GN, antiglomerular basement membrane antibody (anti-GBM) GN, monoclonal Ig GN, and C3 glomerulopathy (Table 1). The classification is primarily on the basis of the findings by immunofluorescence microscopy (IF) or less commonly, immunohistochemistry (IHC) integrated with light microscopy (LM) and electron microscopy (EM).

Immune-complex GN is characterized by granular deposits of polyclonal Ig on IF or IHC. Complement is often codeposited along with the Ig. The type and location of the immune deposits often point to the underlying etiology. Immune-complex GN includes specific disease entities, such as IgA nephropathy, lupus nephritis, and fibrillary GN, with the understanding that fibrillary GN may not represent true immune–complex GN in the sense of antigen-antibody complexes. Immune-complex GN also includes GN resulting from infections and autoimmune diseases other than SLE. Indeed, infections are an important cause of immune-complex GN in both developing and developed countries.

The pattern of glomerular injury is variable, and depending, in part, on the etiology, there may be no lesion by LM, mesangial proliferative, endocapillary proliferative, exudative, membranoproliferative, necrotizing and crescentic, sclerosing, or a combination of these patterns. Some forms of GN (e.g., lupus nephritis) may have mixed membranous and proliferative patterns.

Pauci–immune necrotizing and crescentic GN is characterized by negative or few Ig deposits on IF or IHC, 80%–90% of patients have serologic evidence of ANCA, and as such, this category has been referred to as ANCA-associated GN (ANCA GN) whereas the remaining patients are termed ANCA-negative GN. The principal antigens targeted by ANCA include myeloperoxidase (MPO) and proteinase 3 (PR3). On the basis of the clinicopathologic findings ANCA GN is classified according to the Chapel Hill Consensus as microscopic polyangiitis, granulomatosis with polyangiitis, or eosinophilic granulomatosis with polyangiitis. The diagnosis of ANCA GN should include both the clinicopathologic phenotype and the ANCA specificity (e.g., MPO-ANCA, microsopic polyangiitis). Cellular, fibrocellular, and fibrous crescents may be present depending on the stage of the disease process.

Anti-GBM GN is characterized by linear deposits of Ig, most often IgG, and frequently, C3 along the GBM on IF or IHC, and it is confirmed by detection of circulating anti–GBM antibodies. The linear Ig staining characterizes this form of GN and contrasts with the granular deposits usually seen in immune-complex GN or smudgy deposits seen in fibrillary GN. Most active anti-GBM GN is characterized by a severe necrotizing and crescentic pattern; ≤25% of patients with anti-GBM GN also have circulating ANCA.

Monoclonal Ig GN is characterized by monotypic Ig deposits in the glomeruli and/or along tubular basement membranes on IF or IHC. Monoclonal Ig GN is associated with an underlying monoclonal gammopathy/paraproteinemia in many but not all patients. Specific disease entities in this category that have diagnostic features by IF/IHC and EM include proliferative forms of monoclonal Ig deposition disease, immunotactoid GN, and rare patients of fibrillary GN with monoclonal Ig deposits. In the absence of these distinct patterns, GN with monoclonic Ig glomerular deposits on IF/IHC and mesangial/capillary wall deposits on EM is labeled as proliferative GN with monoclonal Ig deposits. Although a membranoproliferative pattern is most common, other patterns, including mesangial proliferative, diffuse proliferative, necrotizing and crescentic, or sclerosing, may be present.

C3 glomerulopathy is characterized by the presence of dominant C3 deposits in the glomeruli with minimal or no Ig deposits.

### Table 1. Classification of GN

<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>Immune-complex GN</td>
<td>IgA nephropathy, IgA vasculitis, lupus nephritis, infection-related GN, fibrillary GN with polyclonal Ig deposits</td>
<td>Mesangial, endocapillary, exudative, membranoproliferative, necrotizing, crescentic, sclerosing, or multiple&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Oxford/MEST scores for IgA nephropathy</td>
</tr>
<tr>
<td>Pauci-immune GN</td>
<td>MPO-ANCA GN, proteinase 3-ANCA GN, ANCA-negative GN</td>
<td>Necrotizing, crescentic, sclerosing, or multiple&lt;sup&gt;b&lt;/sup&gt;</td>
<td>ISN/RPS class for lupus nephritis</td>
</tr>
<tr>
<td>Anti-GBM GN</td>
<td>Anti-GBM GN</td>
<td>Necrotizing, crescentic, sclerosing, or mixed&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Focal, crescentic, mixed, or sclerosing class (Berden/EUVAS class)</td>
</tr>
<tr>
<td>Monoclonal Ig GN</td>
<td>Monoclonal Ig deposition disease, proliferative GN with monoclonal Ig deposits, immunotactoid glomerulopathy, fibrillary GN with monoclonal Ig deposits</td>
<td>Mesangial, endocapillary, exudative, membranoproliferative, necrotizing, crescentic, sclerosing, or multiple&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>C3 glomerulopathy</td>
<td>C3 GN, dense deposit disease</td>
<td>Mesangial, endocapillary, exudative, membranoproliferative, necrotizing, crescentic, sclerosing, or multiple&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

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.

<sup>a</sup>Some pathologists use the terms immune complex–mediated GN, monoclonal Ig–associated GN, etc. It is up to the discretion of the pathologist to use these terms.

<sup>b</sup>Multiple patterns include two or more patterns of injury. The patterns should be stated (e.g., focal mesangial proliferative, crescentic, and sclerosing or diffuse necrotizing, crescentic, and sclerosing).
guidelines for the primary diagnosis

The primary diagnosis (examples are shown in Table 3) is composed of three or four components in the following order: (1) disease entity or pathogenesis/pathogenic type (when specific disease entity is not known), (2) pattern of glomerular injury, (3) scores and/or class of the disease entity where appropriate, and (4) additional disease-related features. In some instances, when two distinct processes are contributing to the patient’s renal dysfunction, more than one primary diagnosis may be listed in order (e.g., ANCA GN and IgA nephropathy).

First, the disease entity or pathogenesis/pathogenic type should be written. If the disease entity is known, it takes precedence over the pathogenesis/pathogenic type.

Second, the pattern of injury should be listed. The GN may be focal or diffuse and segmental or global. The basic patterns of injury include no lesion by LM, mesangial proliferative, exudative, endocapillary proliferative, membranoproliferative, crescentic, necrotizing, and sclerosing GN.38,39

Table 2. Basic format of kidney biopsy report

| 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.
Some examples of GN diagnoses

(1) IgA nephropathy
   Primary diagnosis: IgA nephropathy
   Pattern of injury: diffuse mesangial and focal segmental endocapillary proliferative and sclerosing GN
   Score/grade: Oxford classification: M1 E1 S1 T1
   Additional features: focal global glomerulosclerosis (20%), moderate tubular atrophy and interstitial fibrosis (30%), mild arteriosclerosis and hyaline arteriolosclerosis
   Secondary diagnoses: diabetic nephropathy, mild

(2) Lupus nephritis
   Primary diagnosis: (1) lupus nephritis and (2) thrombotic microangiopathy
   Pattern of injury: diffuse proliferative and sclerosing GN with focal (10%) cellular crescents
   Score/grade: ISN/RPS class IV-G (A/C)
   Additional features: thrombotic microangiopathy associated with antiphospholipid antibodies/clinical, focal global glomerulosclerosis (10%), mild tubular atrophy and interstitial fibrosis (10%), moderate arteriosclerosis, and moderate hyaline arteriolosclerosis

(3) Hepatitis C–associated immune–complex GN
   Primary diagnosis: immune-complex GN
   Pattern of injury: membranoproliferative GN
   Additional features: with features of cryoglobulinemic GN (hepatitis C/clinical), focal global glomerulosclerosis (20%), moderate tubular atrophy and interstitial fibrosis (30%), moderate arteriosclerosis, and moderate hyaline arteriolosclerosis
   Secondary diagnoses: diabetic nephropathy, moderate

(4) Infection-related GN
   Primary diagnosis: IgA–dominant infection–related GN
   Pattern of injury: diffuse exudative GN
   Additional features: associated with S. aureus cellulitis infection/clinical, focal global glomerulosclerosis (30%), moderate tubular atrophy and interstitial fibrosis (30%), moderate arteriosclerosis, and moderate hyaline arteriolosclerosis
   Secondary diagnoses: diabetic nephropathy, moderate

(5) ANCA GN
   Primary diagnosis: proteinase 3–ANCA GN
   Pattern of injury: necrotizing and crescentic GN
   Prognostic class: focal (≥50% normal glomeruli)
   Additional features: clinicopathologic features of granulomatosis with polyangiitis (proteinase 3 and cytoplasmic ANCA/clinical), focal global glomerulosclerosis (10%), mild tubular atrophy and interstitial fibrosis (10%), mild arteriosclerosis, and moderate hyaline arteriolosclerosis

(6) Anti-GBM GN
   Primary diagnosis: anti-GBM GN
   Pattern of injury: necrotizing and crescentic GN, 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

(7) Monoclonal Ig GN
   Primary diagnosis: monoclonal Ig GN
   Pattern of injury: membranoproliferative GN with intracapillary hyaline thrombi (pseudothrombi)
   Additional features: IgM κ-staining of glomerular intracapillary deposits consistent with type 1 cryoglobulins (Waldenström macroglobulinemia/type 1 cryoglobulins/clinical), focal global glomerulosclerosis (30%), moderate tubular atrophy and interstitial fibrosis (40%), moderate arteriosclerosis, and moderate hyaline arteriolosclerosis

(8) C3 glomerulopathy
   Primary diagnosis: C3 GN
   Pattern of injury: membranoproliferative GN
   Additional features: focal global glomerulosclerosis (20%), mild tubular atrophy and interstitial fibrosis (20%), mild arteriosclerosis, and moderate hyaline arteriolosclerosis

ISN/RPS, International Society of Nephrology/Renal Pathology Society; A/C, active/chronic.
*If MPO/PR3 titers are not known, it is acceptable to label as ANCA GN.

GUIDELINES ON SECONDARY DIAGNOSES

Secondary diagnoses include coexisting lesions that do not form the primary diagnosis. These include underlying glomerular diseases, such as diabetic glomerulosclerosis and thin GBM nephropathy. Similarly, tubulointerstitial or vascular findings unrelated to the primary diagnosis, such as drug–induced interstitial nephritis, acute tubular injury, atheroembolic disease, etc., should also be listed as secondary diagnoses. However, glomerular findings etiologically related to the primary diagnosis, such as thrombotic microangiopathy in lupus nephritis, should be included within the primary diagnosis with a clinical modifier, such as lupus anticoagulant/clinical or anticardiolipin antibody/clinical if these are known (Table 3, example 2). Tubulointerstitial thrombotic microangiopathy is associated with antiphospholipid antibodies in lupus nephritis should be included here if it is felt that these reflect a component of the primary disease.

Additional features also include the proportion of globally sclerotic glomeruli, extent of interstitial fibrosis and tubular atrophy (IFTA), and severity of vascular changes, including arterial intimal sclerosis (arteriosclerosis) and arteriolar thickening and hyalinization (arteriolosclerosis). The severity of vascular sclerosis may be reported as mild, moderate, or severe.

Although the report deals with GN, chronic changes may result from additional lesions present on the biopsy. In such patients, the contribution of the separate lesions to the chronic changes may be mentioned in the comment section.

The distinct advantage of this format of reporting is that it is etiology and pathogenesis oriented. The report is adaptable to include new diseases, it is suitable to fit databases, and it is standardized and most importantly, patient centered by providing relevant information for targeted, mechanism–based treatment approaches.
Table 4. Definitions of glomerular lesions derived from the Oxford classification of IgA nephropathy\textsuperscript{1,64} and patterns of GN derived from the ISN/RPS lupus classification\textsuperscript{22}

<table>
<thead>
<tr>
<th>Glomerular lesions</th>
<th>Mesangial hypercellularity</th>
<th>Cellular crescent</th>
<th>Fibrocellular crescent</th>
<th>Fibrous crescent</th>
<th>Endocapillary hypercellularity</th>
<th>Fibrinoid necrosis</th>
<th>Tubulointerstitial process</th>
<th>Sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;3 Mesangial cells per mesangial area</td>
<td>Extracapillary cell proliferation of more than two cell layers with &gt;50% of the lesion occupied by cells</td>
<td>An extracapillary lesion comprising cells and extracellular matrix, with &lt;50% cells and &lt;90% matrix</td>
<td>Extracapillary crescents with &gt;90% matrix</td>
<td>Hypercellularity caused by an increased no. of cells within glomerular capillary lumina, causing narrowing of the lumina</td>
<td>Disruption of the GBM with fibrin exudation</td>
<td>Obliteration of the capillary lumen by increased extracellular matrix with or without hyalinosis or foam cells</td>
<td></td>
</tr>
</tbody>
</table>

**Patterns of GN**

- **Minimal mesangial GN**: Normal glomeruli by LM but mesangial immune deposits by IF
- **Mesangial proliferative GN**: Purely mesangial hypercellularity
- **Active (proliferative) GN**: Any or all of the following glomerular lesions: endocapillary hypercellularity, karyorrhexis, fibrinoid necrosis, rupture of GBMs, cellular or fibrocellular crescents, subendothelial deposits identifiable by LM, and intraluminal immune aggregates
- **Necrotizing GN**: Segmental or global fibrinoid necrosis
- **Crescentic GN**: >50% Glomeruli with cellular, fibrocellular, or fibrous crescents (with percentage of crescents always noted in the diagnostic line, even when <50%)*
- **Membranoproliferative GN**: Mesangial and/or endocapillary hypercellularity and thickening of capillary walls caused by subendothelial Ig and/or complement factors
- **Exudative GN**: Neutrophils accounting for >50% of glomerular hypercellularity
- **Sclerosing GN**: Any or all of the following glomerular lesions: glomerular sclerosis, fibrocellular crescents, subendothelial deposits, and/or complement factors

\textsuperscript{22}ISN/RPS, International Society of Nephrology/Renal Pathology Society.

\textsuperscript{*}Except for the first two patterns, multiple patterns can occur together in a single specimen (derived from the ISN/RPS lupus classification\textsuperscript{22}).

\textsuperscript{22}The term crescentic GN is used when crescents are present in at least 50% of glomeruli, and applies to immune-complex GN/C3 glomerulopathy. This does not apply to ANCA GN and anti-GBM GN, where less than 50% of the glomeruli may be involved by crescents.

inflammation or acute tubular injury that is a component of the primary disease may be listed with the primary diagnosis or simply described in the LM report (e.g., mild to moderate inflammation that often accompanies crescentic and other severe forms of GN). This is at the discretion of the renal pathologist and should relate to the severity of the tubulointerstitial process and its perceived contribution to the patient's clinical presentation.

Also note that, although the main focus of the report is on GN, a nonproliferative glomerular, tubulointerstitial, or vascular lesion may be the primary diagnosis in light of the clinical indications of the biopsy, and the GN may be the secondary diagnosis; also, there may be more than one primary diagnosis if the pathologist feels that they are of similar clinical importance (Table 3, example 2).

**GUIDELINES ON COMMENT**

The comment should summarize the biopsy findings and discuss their implications and how they relate to the clinical presentation. If required, a differential diagnosis of the findings may be included with a discussion of why one diagnosis might be favored and the evidence supporting or opposing each potential diagnosis. If pertinent, the comment should explain the score/grade, prognosis of the disease, and risk of recurrence in renal allografts. Key literature references may be added in this section.

**GUIDELINES ON CLINICAL DATA**

A brief overview of the clinical data should be included in the report. These data must be provided by the nephrologist who submits the specimen for pathologic evaluation. These consist of the patient’s age, sex, ethnicity, acute kidney disease versus CKD, and indication for the kidney biopsy (e.g., hematuria, proteinuria, elevated creatinine, or others [for example, biopsy for prognostic purposes]). Pertinent clinical findings, such as fatigue, edema, shortness of breath, hemoptysis, rash, infection, etc., should be included. Coexisting diseases, such as diabetes, hypertension, and lymphoproliferative disorders, and a brief drug history (including pertinent past exposures) should be mentioned as well as any relevant family history. Laboratory findings to be included are serum creatinine, urinalysis and proteinuria per 24 hours or urine protein-to-creatinine ratio, serum complement levels (C3 and C4), protein electrophoresis, and serologic findings, such as antinuclear antibody and anti-double stranded DNA titers, ANCA (anti-MPO and anti-PR3), hepatitis serologies, and cryoglobulin titers as appropriate. Any pertinent microbiology results should be stated.

**GUIDELINES ON GROSS DESCRIPTION**

The number, size of cores, and fixative(s) in which the tissue is received for LM, IF, and EM should be stated. Poorly preserved tissue (e.g., dry tissue with no fixative or leaking fixative) should be documented. Documentation should be made if tissue from a single (e.g., formalin) vial is allocated for EM as well as LM.
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 mesangiolysis</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>
</tr>
<tr>
<td>Disruption of Bowman’s capsule</td>
</tr>
</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>
<tr>
<td>Vessels</td>
</tr>
<tr>
<td>Arteritis, emboli, and thrombosis</td>
</tr>
<tr>
<td>Arteriosclerosis and arteriolosclerosis: absent, mild, moderate, or severe</td>
</tr>
</tbody>
</table>

GUIDELINES ON LM REPORT

General guidelines for LM examination of medical renal biopsies have been described by Chang et al., and essential information to be included in the biopsy report is summarized in Table 5; we will focus here on those aspects most specific to evaluation of GN. The pattern of injury should be described, including whether the lesion is focal or diffuse and segmental or global. Key features include mesangial and endocapillary hypercellularity; infiltration of capillary tufts by leukocytes and whether these are mononuclear cells, neutrophils, or both; presence of necrosis; karyorrhexis and/or crescents; and rupture of GBMs and/or Bowman’s capsule. Crescents may be cellular, fibrocellular, or fibrous, and they may be segmental or circumferential (or nearly so). The percentage of glomeruli involved by crescents should be mentioned. Lobular accentuation of the glomerular tufts may be present. Mesangial expansion and capillary wall thickening should be mentioned. Intracapillary fibrin thrombi, hyaline thrombi (pseudothrombi), and wire loops should be noted. The presence of GBM changes, such as vacuoles/pinholes, spikes, or double contours, should be described.

Next, the tubular and interstitial pathology should be described. This includes interstitial inflammation, characteristics of the infiltrate, and presence or absence of granulomas. The location of the infiltrates (i.e., in preserved areas or areas of IFTA) should be mentioned. To indicate the severity of IFTA, which is a key prognostic indicator in many if not all forms of GN, the estimated percentage of IFTA in the cortical area should be given (rounded off to the nearest 5% or 10%). Grades of IFTA scored as mild (10%–25%), moderate (26%–50%), and severe (>50%) are an acceptable form of reporting, with the percentages mentioned in parentheses after the grade. If the amount of interstitial (mononuclear cell) infiltrate is concordant with the amount of IFTA and limited exclusively or mainly to areas of IFTA, it should not be described as a chronic interstitial nephritis to avoid the misinterpretation that a separate or superimposed interstitial nephritis is present. If it seems evident that an interstitial nephritis is present and distinct from the chronic fibrotic changes, this should be described here but also, listed as a secondary diagnosis, with its differential diagnosis given in the comment.

Finally, vascular lesions should be described. Lesions most pertinent to GN include arteritis, thrombotic microangiopathy, and arterio- and arteriolosclerosis caused by hypertension associated with the GN. The severity of vascular sclerosis may be reported as mild, moderate, or severe.

GUIDELINES ON IF REPORT

Again, we will focus on those aspects most specific to evaluation of GN; for general guidelines, refer to the work by Chang et al. and Table 6, which summarize essential information to be included in the biopsy report. The optimum panel of stains includes IgG, IgM, IgA, C3, C1q, fibrinogen, albumin, and κ- and λ-light chains, and the report should separately address findings in glomeruli, tubules, interstitium, and blood vessels. The results can be reported in paragraph or tabular form at the discretion of the renal pathologist.

For glomerular staining, the report should clearly state whether staining for each immune reactant is seen in some or all glomeruli, whether this is segmental or global, and the location(s) of staining within glomeruli: mesangial, capillary wall, or both. The results should also specify the type of staining. Potential descriptors include (1) granular, (2) semilinear (e.g., for conditions associated with subendothelial deposits, including immune-complex GN with a membranoproliferative pattern and diffuse proliferative lupus nephritis), (3) coarsely granular (e.g., infection-related GN), (4) linear (e.g., anti-GBM GN and monoclonal Ig deposition disease), and (5) smudgy (e.g., fibrillar GN). Importantly, segmental staining for IgM, C3, and occasionally, C1q is common in areas of segmental sclerosis; this finding should not be described with any of the descriptors provided above. One
possible terminology is segmental glomerular tuft, avoiding the need to specify as mesangial or glomerular capillary wall. The overwhelming majority of biopsies will exhibit at least mild staining for C3 in blood vessels, and tubular casts nearly always will stain for κ- and λ-IgA. It is important to maintain awareness of these as internal positive controls.

**KEY DISEASE-SPECIFIC COMMENTS**

The type, relative intensity, and pattern of distribution of the various immune reactants are critical to properly diagnose the type of immune-complex GN. Thus, IgA nephropathy is characterized by the presence of mesangial dominant or co-dominant IgA; lupus nephritis is characterized by presence of mesangial and/or capillary wall deposits of multiple classes of Ig, including IgG, IgA, IgM, and Sjögren syndrome by IgM/IgG; and infection-related GN is usually associated with capillary wall deposits of IgG/IgM in many bacterial infections, dominant IgA in staphylococcal infections, and IgM/IgG in viral infections. C3 is often present and less commonly, C1q along with the Ig in most patients of immune-complex GN.

In pauci-immune GN, the intensity of staining for Ig and complement is typically in the range of negative to 1+ but can reach 2+ in areas of necrosis. Greater intensity of staining or staining for IgA or IgG in areas not involved by necrosis should raise the possibility of the overlap of two separate disease processes (e.g., ANCA GN and IgA nephropathy or ANCA GN and membranous glomerulopathy). Fibrinogen may be present in the distribution of glomerular necrotizing lesions and/or crescents.

Anti-GBM GN is defined by intense and diffuse linear staining for IgG along the GBM. There is linear GBM staining for κ- and λ-light chains with similar intensity. Rarely, linear staining for monoclonal IgG occurs, or linear IgA rather than IgG may be present, indicating an IgA class of anti-GBM antibodies. C3 is often present in a semilinear or granular pattern along the glomerular capillary walls. To avoid confusion with anti-GBM GN, the linear staining seen in diabetic glomerulosclerosis can be called linear accentuation, which is commonly observed for IgG and albumin.

Monoclonal Ig GN is characterized by monotypic Ig deposits in the glomeruli. In the setting of proliferative GN with monoclonal Ig, the deposits frequently stain for a heavy chain (most commonly, IgG, less commonly, IgM, and rarely, IgA) and one of the light chains, either κ and λ. In some instances, the monotypic deposits may be composed of either a heavy or light chain only. One caveat is that λ-staining may significantly exceed κ-staining in IgA nephropathy. Granular C3 is often present along the monoclonal Ig.

If the intensity of staining for C3 exceeds the intensity of staining for all other immune reactants by two orders of magnitude (i.e., 3+ versus 1+ and 2+ versus ±), the most likely diagnosis is C3 glomerulopathy or an infection-related GN if an obvious history of infection is present.

Awareness of situations in which positive staining may be incorrectly interpreted as signifying immune-complex GN is essential. Examples include (1) C3 and IgM in areas of segmental scarring or segmental sclerosis, (2) IgG in areas of fibrinoid necrosis in ANCA GN, and (3) IgG and/or IgA in protein droplets within podocytes in proteinuric states.

Ischemic and sclerosed glomeruli may be negative for Ig in immune-complex GN.

**GUIDELINES ON EM REPORT**

EM is a crucial diagnostic tool for glomerular diseases. Data indicate that 20% of renal biopsies cannot be accurately diagnosed without EM, and nearly all of these are glomerular diseases.30 Processing a sample of renal cortex for EM is recommended for all native renal biopsies. Although there is a small subset of glomerular diseases for which, when diagnostically well established by LM and IF or IHC, elective deferment of EM might be considered, this is done at a risk of missing possible underlying pathology (e.g., early changes of diabetic nephropathy). Examination of stained 1-μm-thick sections of tissue processed for EM should be considered as part of the histologic examination of the biopsy and should be done by the pathologist and not by a technologist. Glomeruli selected for EM study should be representative of the LM findings, and glomeruli showing global or extensive segmental sclerosis or ischemic changes should be avoided. If the EM sample contains no glomeruli or only sclerotic/ischemic glomeruli, paraffin-embedded tissue should be reprocessed for EM when possible. Exceptions to this would be in patients with a diagnosis that is well established by LM and IF/IHC; EM on deparaffinized tissue with its inherent limitations (e.g., accurate determination of GBM thickness) is unlikely to add additional diagnostic information.

The EM portion of the biopsy report may be written in narrative or tabular form and should contain the number of blocks processed, the number of blocks cut, the total number of glomeruli on 1-μm sections cut from these blocks, the number of globally and segmentally sclerotic glomeruli, the number(s) of glomeruli with other lesions (e.g., crescents), and tubulo-interstitial and vascular lesions if present. EM findings pertinent to GN to be included in the biopsy report are summarized in Table 7.

**Table 7. Guidelines for EM**

<table>
<thead>
<tr>
<th>No. of glomeruli studied by EM, including no. of globally sclerosed or with other evident lesions</th>
<th>Glomerular deposits: location, type, quantity, size, and substructure</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBM: architecture, thin/thick, duplication, ischemic changes, and rupture</td>
<td>Endothelium: fenestrations, swelling, and presence of tubulointerstitial inclusions</td>
</tr>
<tr>
<td>Mesangial matrix: normal/increased and mesangiolysis</td>
<td>Mesangial cellularity: normal/increased</td>
</tr>
<tr>
<td>Mesangial matrix: normal/increased and mesangiolysis</td>
<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>
<td>Tubular epithelial and basement membrane abnormalities when present</td>
</tr>
</tbody>
</table>
KEY DISEASE–SPECIFIC COMMENTS

EM studies are helpful in confirming the electron dense deposits of immune-complex GN, monoclonal Ig GN, and C3 glomerulopathy.

Immune-complex GN is characterized by mesangial and/or capillary wall electron dense deposits. Endocapillary proliferative and membranoproliferative patterns of injury are associated with capillary wall deposits, usually subendothelial and in some patients, intramembranous and subepithelial. However, a mesangial proliferative pattern of injury is usually associated with mesangial deposits. Subepithelial humps are typically seen in infection-related GN but may be present in C3 glomerulopathy as well.9,11,39,52,53 Fibrillary GN is characterized by deposits of nonbranching, randomly oriented fibrils with a diameter typically exceeding that of amyloid fibrils (generally 15–24 nm). Tubular substructures may be present indicating cryoglobulins, and other substructures, such as fingerprints, suggest an autoimmune disease along with tubuloreticular inclusions (IFN signature) in endothelial cells.

ANCA GN and anti-GBM GN show few or no electron dense deposits but may show crescents/fibrinoid necrosis with fibrin in the glomerular tufts/Bowman’s space.

EM findings are variable in monoclonal Ig GN.4 Mesangial and mostly, subendothelial and less commonly, subepithelial electron dense deposits are present in proliferative GN with monoclonal Ig deposits.29,30 Punctate, finely granular deposits in the mesangium along the inner (subendothelial) aspect of GBMs and in tubular basement membranes are present in monoclonal Ig deposition disease. However, microtubules measuring 20–60 nm, often in parallel arrays, are present in immunotactoid glomerulopathy. Substructures may also be present in deposits in monoclonal Ig GN, particularly when cryoglobulins are present.

For C3 glomerulopathy, dense deposit disease is characterized by highly osmiophilic intramembranous, continuous, or interrupted band–like deposits involving large segments of the GBM.39 The deposits are also found as rounded deposits in the mesangium and in many patients, Bowman’s capsule and tubular basement membranes. However, C3 GN is characterized by mostly mesangial and subendothelial and sometimes, intramembranous and subepithelial deposits. In some patients, there may be multiple layers of electron dense deposits and basement membrane material, resulting in thickening and fraying of the GBMs. The deposits appear less discrete, more ill-defined, and confluent compared with the electron dense deposits of immune-complex GN.

GUIDELINES ON USE OF ANCILLARY STUDIES

These include IF on pronase–digested paraffin material (or possible IHC on paraffin material), IgG subclass determination by IF, C4d staining in GN, and mass spectrometry to determine the composition of deposits.29,55–61 The recommendations for ancillary studies are strong (A; established as contributory to diagnosis or prognosis), moderate (B; probably contributory to diagnosis or prognosis), possibly contributory to diagnosis or prognosis (C), and insufficient data (U).

When frozen tissue is not available for IF, salvage techniques should be available. These include IF after pronase digestion using formalin–fixed, paraffin–embedded tissue or immunoperoxidase staining on paraffin-embedded material. Recommendation: A.

Subtyping of IgG (i.e., IgG1, IgG2, IgG3, and IgG4) should be performed in patients with monoclonal IgG GN. Recommendation: A.

The salvage technique of pronase digestion may also be used in some instances where masked monoclonal Ig deposits are suspected in setting of monoclonal gammopathy and when routine IF studies are negative but EM studies show electron dense deposits. Recommendation: C.

C4d stain to distinguish immune-complex GN versus C3 glomerulopathy. Recommendation: C.

C4d as a prognostic marker for IgA nephropathy. Recommendation: C.

Mass spectrometry to determine the composition of deposits. Recommendation: U.

SUMMARY

This manuscript provides guidelines for classification, diagnosis, and reporting of GN. The main conclusion of the consensus meeting was that the kidney biopsy report should be etiology and pathogenesis driven. The kidney biopsy diagnosis should consist of a primary diagnosis that includes the disease entity or pathogenic type (if disease entity is not known) followed by pattern of injury, a score/grade of the disease if appropriate, and additional findings directly related to the primary disease entity. The diagnosis should also include separate secondary diagnoses if present. Guidelines for LM, IF, and EM and ancillary studies are also provided. This should be regarded as a working document, much like the Banff classification for renal allograft pathology, subject to modification at future meetings and as new data evolve regarding the pathogenesis of and relationships between different glomerular diseases. The flexibility of the Banff schema has been one of its greatest strengths; whereas the initial version of that classification, like this document, was on the basis of consensus opinions of experts in the field rather than actual data, later iterations of Banff have been more data driven.

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REFERENCES


