A Systematic Method for Categorizing GN

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In the 1820s, the diagnosis of glomerular disease was strictly clinical and on the basis of clinical presentation and the presence of proteinuria, which was conveniently determined by placing a lit candle under a spoon of urine to determine if it congealed into a protein-rich precipitate on heating. A great leap forward was the introduction of the kidney biopsy in the 1950s by Kark and Muehrke,¹ which allowed early characterization of renal disease into a proliferative form (type 1) or acute GN and a nonproliferative form (type 2) GN associated with nephrotic syndrome.² With the advent of immunofluorescence and electron microscopy in the 1960s, the renal biopsy became key to the diagnosis of glomerular disease. Categorizing the type of GN has often been challenging to the clinician, because the diagnosis is sometimes on the basis of clinical presentation (e.g., rapidly progressive GN), sometimes etiology based (e.g., poststreptococcal GN), and sometimes histologic based (pauci-immune GN). To further complicate matters, there has been no standardized method for how renal pathologists should report renal biopsy findings.

To address these shortcomings, the Mayo Clinic convened a group of experts that included nephrologists and renal pathologists to develop working recommendations to standardize renal biopsy findings for subjects with GN. For this purpose, GN is viewed as a lesion showing hypercellularity caused by either an increase in endogenous glomerular cells or the infiltration of leukocytes. Specifically, GN does not include diseases associated with normocellularity, such as minimal change disease, membranous nephropathy, and amyloid. Five general categories of GN were identified, including (1) immune complex GN (such as IgA nephropathy and lupus nephritis), (2) pauci-immune GN (such as ANCA-associated GN), (3) antiglomerular basement membrane GN, (4) monoclonal Ig–associated GN (such as variants of light chain deposition disease), and (5) C3 glomerulopathy (including dense deposit disease and C3 glomerulopathy). For each of these basic categories, the disease is further categorized with a primary diagnosis that is on the basis of the disease entity or pathogenesis (such as lupus nephritis) followed by a description of the pattern of histologic injury; the score, grade, or class; and the presence of additional features, such as the degree of activity or chronicity. The authors³ suggest that a standardized method for reporting renal biopsy findings will have a variety of benefits, including providing more detailed information to the treating clinician, which may aid in understanding the pathogenesis or etiology, and providing a standardized categorization that will allow better potential to incorporate the findings into a database for registry or research purposes.

All in all, the proposal is well overdue and highly commended. Moving away from histologic patterns to etiology- and pathogenesis-based diagnoses should lead to better management and treatment. One particularly good aspect of the new system is the separation of diseases associated with monoclonal gammapathies and the diseases associated with only complement deposition from the other groups, because these conditions really require different approaches to therapy. Clinical modifiers can be added that suggest the underlying etiology, which might affect treatment. For example, categorizing immune complex proliferative GN on the basis of etiologies also highlights different management approaches, such as that the treatment of GN varies markedly on the basis of whether it is caused by active bacterial infection (endocarditis), postinfectious (poststreptococcal), viral (hepatitis C virus), or autoimmune (lupus) etiologies.

One potential limitation is in the ownership of the diagnosis. Historically, the renal pathologist describes the histologic findings, and although this is sometimes sufficient to make an etiologic diagnosis, often, it is the nephrologist who finalizes the diagnosis on the basis of the clinical, laboratory, and renal biopsy findings. This is particularly true when key laboratory studies are pending at the time that the biopsy is taken (for example, ANCA serologies). An aspect of the new classification system is that it requires the renal pathologist to work with the nephrologist closely to share both the clinical information and biopsy findings, allowing the pathologist to provide the diagnosis. This is, of course, ideal, because the discussion should be two way and represent the thinking of both specialists. Nevertheless, it will ultimately fall on the nephrologist to determine

Published online ahead of print. Publication date available at www.jasn.org.

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the final diagnosis and treatment plan, especially in those situations in which key laboratory data are unavailable at the time of biopsy.

Another limitation is potential cross-over—how does one characterize a patient with lupus who has features of membranous nephropathy and diffuse proliferative GN or a patient with such exuberant cryoglobulinemic hepatitis C virus–associated GN that there are minimal IgG and IgM deposits because of rapid removal by infiltrating macrophages? The new system, however, does provide some flexibility in describing these features by allowing secondary diagnoses. The minimal number of glomeruli required on the biopsy to distinguish focal from diffuse disease might be considered, and also, the effect of patient age on secondary diagnoses, such as glomerulosclerosis, should be entertained.

Although there may be some challenges with the new classification system, it definitely is a progressive step forward. This new working classification system for categorizing the types of GN should be of immense help to the clinician in guiding treatment. A more detailed and standardized biopsy report will also aid with clinical and translational glomerular studies. We predict that, as molecular markers become better defined, they will be added to this working document to better inform diagnosis, prognosis, and hopefully, precision-based treatment. Indeed, it is reminiscent (as noted by the authors) of the Banff Classification System for categorizing renal transplant biopsies, which has also helped the transplant nephrologist in management. Let us hope that this new approach has the same result.

DISCLOSURES
None.

REFERENCES

Amniotic Fluid Stem Cells within Chimeric Kidney Rudiments Differentiate to Functional Podocytes after Transplantation into Mature Rat Kidneys

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doi: 10.1681/ASN.2015101115

The pioneering work of Grobstein, Saxen, and Sariola led to the development of culture systems that could support the growth and differentiation of mouse kidney rudiments in vitro. Cultured kidney rudiments can be easily manipulated, either genetically or by the application of growth factors, inhibitors, or other small biologic substances, and are thus useful model systems for investigating the mechanisms that regulate the development of the mammalian kidney. Kidney rudiments have also been evaluated for their potential to integrate into mature kidneys and treat renal insufficiency. Woolf et al. showed that rudiments transplanted into neonatal mouse kidneys generated functional nephrons with filtering capacity, with a subsequent study by Rogers and Hammerman showing that transplanted rudiments could improve survival in anephric rats, albeit for only a few days. However, despite these promising results, another study by Ashton and co-workers showed that although the kidney rudiments continued to develop for a few weeks after transplantation, by 3 months, their level of maturity only reached that of early neonatal kidneys. This meant that the GFR of the transplanted rudiments was equivalent to only 2% of the GFR of an adult rat kidney, which explains why the rudiments were unable to sustain life in anephric rodents beyond a few days.

Although these studies suggest that kidney rudiments are unlikely to have much therapeutic value when transplanted into diseased kidneys, they can nevertheless be very effective tools for assessing the nephrogenic potential of various types of stem and progenitor cells. For instance, following the work of Atala and co-workers, who found that disaggregated metanephroi isolated from bovine embryos could self-organize to form functioning nephrons, Unbekandt and Davies developed an assay that involved disaggregating mouse kidney rudiments to single cells, combining them with exogenous stem/progenitor cells, and then allowing the cells to reaggregate to form chimeric kidney rudiments. These chimeric rudiments