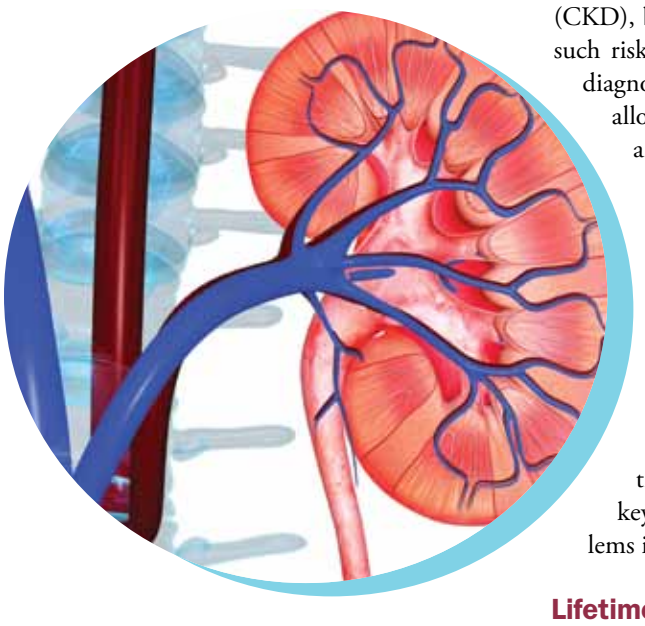
ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KidneyNews

July 2014 | Vol. 6, Number 7

Risk Factors for Chronic Kidney Disease Evident Decades Before Diagnosis



Risk factors for many chronic diseases are present well before any signs of a problem. Age, hypertension, ethnicity, diabetes, smoking, low HDL cholesterol, proteinuria, and obesity all have been identified as risk factors for chronic kidney disease (CKD), but most studies have evaluated such risk factors at or near the time of diagnosis. Earlier identification may allow for risk factor modification and disease prevention.

Researchers have now found that certain factors are present and identifiable 30 years or more before a diagnosis of CKD. The findings, which are published in the *Journal of the American Society of Nephrology*, suggest that obesity, high blood pressure, high triglycerides, and diabetes are key signs of potential kidney problems in the future.

Lifetime risks revealed

To look at risk factors for CKD that may appear well in advance of kidney disease, Caroline S. Fox, MD, MPH, and Gearoid McMahon, MB, BCh, of the National Heart Lung and Blood Institute's Framingham Heart Study and the Center for Population Studies led a team that examined risk factors in study participants who did and did not develop kidney disease.

"One of the benefits of the Framingham Heart Study is that we have a very long duration of follow-up," Fox said. "As a result, we are able to look far back in time prior to when individuals develop a disease to examine their risk factors."

The researchers identified 441 new cases of CKD among participants of the Framingham Heart Study, and they matched them with 882 controls who did not develop CKD. Those who ultimately developed CKD were 76 percent more likely to have had hypertension, 71 percent more likely to have been obese, and 43 percent more likely to have had higher triglycerides 30 years before CKD diagnosis.

They were also 38 percent more likely to have had hypertension, 35 percent more likely to have had higher triglyceride levels, and nearly three times more likely to have had diabetes 20 years before CKD diagnosis. There was a graded increase in CKD risk with each additional risk factor in any combination,

Continued on page 3

Medicaid Expansion May Reduce Access Gaps in Kidney-Related Care, Study Suggests

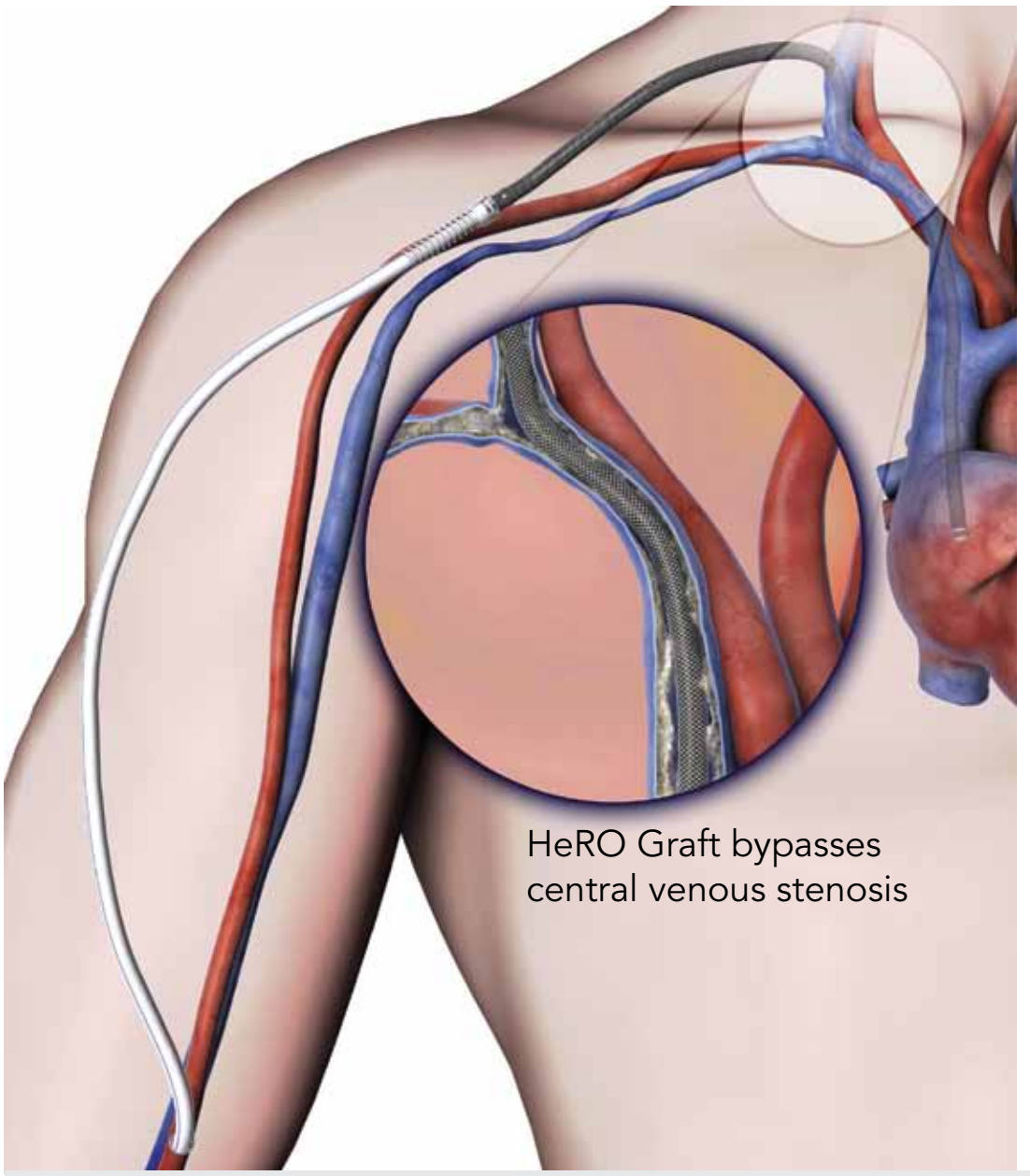
While Medicaid is designed to provide health insurance for low-income Americans, states have flexibility within federal guidelines to design their programs. There is limited information on how differences in Medicaid coverage influence chronic disease care. Now a study shows that states with broader Medicaid coverage have lower incidences of kidney failure and smaller insurance-related gaps in access to kidney disease care. The *Journal of the American Society of Nephrology* findings point to the potential benefits of Medicaid expansion on the prevention and management of a chronic disease.

Chronic disease care is a major source of rising health care expenditures, and access to care for uninsured individuals with a chronic disease has eroded over the last decade. This may change for many patients with the implementation of the Affordable Care Act, which expands Medicaid coverage to adults with incomes below 133% of the federal poverty level; however, not all states are expected to participate in this expansion.

Examining the care of patients approaching end stage renal disease (ESRD) may provide insights into the potential effect of Medicaid expan-

Continued on page 3

Inside



HeRO Graft bypasses central venous stenosis

HeRO (Hemodialysis Reliable OutFlow) Graft is the **ONLY** fully subcutaneous AV access solution clinically proven to maintain long-term access for hemodialysis patients with **central venous stenosis.**

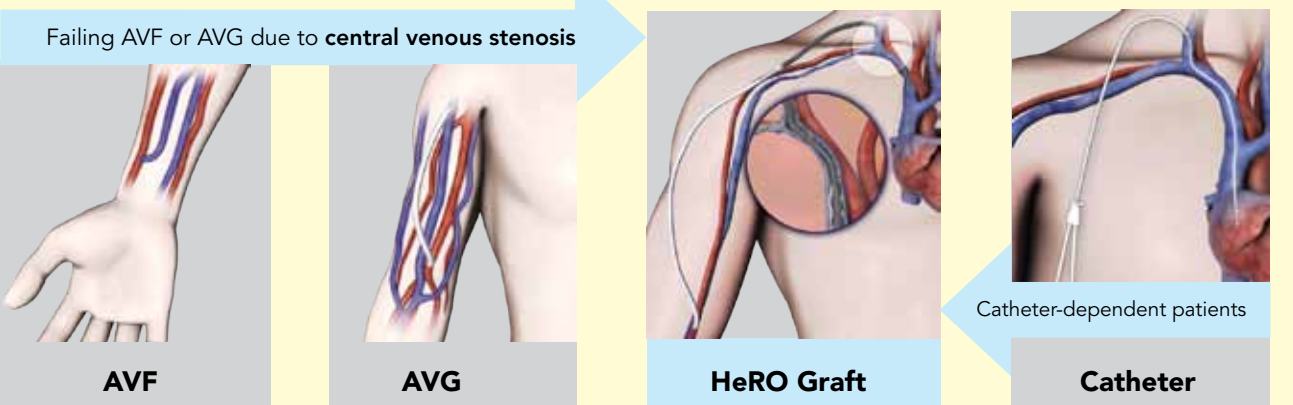
- **Fewer Infections:** 69% reduced infection rate compared with catheters[1]
- **Superior Dialysis Adequacy:** 1.7 Kt/V, a 16% to 32% improvement compared with catheters[1]
- **High Patency Rates:** Up to 87% cumulative patency at 2 years[1, 2]
- **Cost Savings:** A 23% average savings per year compared with catheters[3]

Reducing Catheter Dependency

HeRO Graft Candidates

- Catheter-dependent or approaching catheter-dependency
- Failing AVF or AVG due to central venous stenosis

Treatment Algorithm



Learn more at **www.herograft.com**
Order at: **888.427.9654**

References:
1) Katzman et al., J Vasc Surg 2009. 2) Gage et al., EJVES 2012. 3) Dageforde et al., JSR 2012.

Indications for Use: The HeRO Graft is indicated for end stage renal disease patients on hemodialysis who have exhausted all other access options. See Instructions for Use for full indication, contraindication and caution statements. Rx only.

HeRO Graft is classified by the FDA as a vascular graft prosthesis.

1. Download the App
2. Scan the code with your mobile device to watch video

Get the free mobile app at
http://gettag.mobi

1655 Roberts Boulevard, NW • Kennesaw, Georgia 30144 • Phone (888) 427-9654 • (770) 419-3355

CryoLife®
Life Restoring Technologies®

Early Risk

Continued from page 1

indicating that the more risk factors an individual had in the past, the more likely they were to develop kidney disease.

Mechanisms and implications

Fox and her colleagues explored the potential mechanisms behind the links they found. For example, regarding dyslipidemia, research indicates that the accumulation of both triglycerides and the breakdown products of lipid metabolism in the blood have atherogenic and pro-inflammatory effects on the vasculature in the kidney. Obesity is also known to have detrimental effects on the kidneys, and studies have pointed to histopathological changes of obesity-related glomerulopathy in obese patients with no evidence of renal disease. Also, weight loss in patients with obesity-related kidney disease has been linked with reduced glomerular hyperfiltration and albuminuria.

The authors stressed that their observational study does not show whether altering these risk factors will definitely prevent future disease. Therefore, future studies should focus on whether early risk factor modification will decrease the incidence of CKD. Another important limitation is that the population studied was exclusively European-American, which indicates that the results may not be generalizable to the entire population.

Others in the field noted the value of uncovering early indications of CKD decades before disease onset.

"This is an important study because it provides further evidence that CKD is a life course illness that often develops over several decades. The observation that risk factors such as hypertension, obesity, dyslipidemia, and diabetes may be present two to three decades before the detection of CKD implies that early intervention to abrogate these risk factors may be effective in reducing the prevalence of CKD," said Maarten Taal, MD, FCP(SA), FRCP, a professor of medicine at the University of Nottingham and an honorary consultant nephrologist and lead clinician within the renal unit at the Royal Derby Hospital, in the UK. "This is important because of the high prevalence of CKD that affects up to 15 percent of the adult population and because of the relative ineffectiveness of currently available therapies to ameliorate the associated risks of progressive kidney damage and cardiovascular disease."

Taal noted that the risk factors identified are equally important for cardiovascular disease prevention, so programs focused on cardiovascular risk reduction in the general population should also reduce kidney-related risks.

Study co-authors include Sarah Preis, ScD, PhD, and Shih-Jen Hwang, PhD.

Disclosures: The authors reported no financial disclosures.

The article, entitled "Mid-Adulthood Risk Factor Profiles for CKD," is online at http://jasn.asnjournals.org/.

Medicaid Expansion

Continued from page 1

sion on chronic disease care. Affecting more than 350,000 nonelderly Americans, ESRD comes with a cost of $10 billion per year. While all Americans with ESRD can qualify for Medicare coverage, those who are younger than 65 years must rely on other sources of insurance or pay out of pocket to cover pre-ESRD care. Research indicates that an estimated 10% of adults with nondialysis-dependent chronic kidney disease are uninsured.

Using national data, Manjula Tamura, MD, MPH, of the VA Palo Alto Health Care System and Stanford University, led a team that assessed the relation between the extent of state Medicaid coverage and access to care among nonelderly adults approaching ESRD and whether that relationship differed based on patients' insurance status. "We wanted to determine whether states with broader Medicaid coverage of low-income non-elderly adults had a lower incidence of ESRD and better access to pre-ESRD care," Tamura said. "We also wanted to determine whether broad state Medicaid coverage benefited uninsured adults in addition to those receiving Medicaid."

The researchers identified 408,535 adults aged 20 to 64 years who developed ESRD from 2001 through 2008. Medicaid coverage among low-income nonelderly adults living in different states ranged from 12.2% to 66.0%. Broader Medicaid coverage among low-income nonelderly adults was associated with a lower incidence of ESRD: for each additional 10% of the low-income nonelderly population covered by Medicaid, there was a 1.8% decrease in ESRD incidence.

Low-income nonelderly adults with ESRD who were on Medicaid had better access to care in states with broader Medicaid coverage: For a 50-year-old white woman, the access gap to being put on the kidney transplant waiting list between Medicaid and private insurance decreased by 7.7 percentage points in high vs. low Medicaid coverage states. Similarly, the access gap to transplantation decreased by 4.0 percentage points and the access gap to peritoneal dialysis decreased by 3.8 percentage points. Finally, broader Medicaid coverage was associated with some spillover benefits for uninsured adults with ESRD, but these were small and not consistently observed.

"Our study suggests that Medicaid expansion among low-income nonelderly adults could support efforts to prevent kidney failure and improve access to kidney disease care," Tamura said.

The findings are consistent with other recent studies that found lower rates of adult mortality and delayed care in states that expanded Medicaid coverage, and improvements in mental health among newly enrolled Medicaid beneficiaries.

In an accompanying editorial, Rajnish Mehrotra, MD, and Larry Kessler, ScD, of the University of Washington, Seattle, stated that the researchers' work "highlights the intricate web of health insurance, access to care, and ESRD. Their study is timely as a social experiment is unfolding in this country that will allow us to further examine the association between Medicaid coverage and health care outcomes." They noted that such a population-level analysis needs corroborative evidence to identify the causes for the links that were found, though. For example, improved treatment for diabetes and hypertension, which are the most common underlying causes of ESRD, may have considerable impacts on the association of more generous state Medicaid coverage with lower incidences of ESRD.

Because a 2012 Supreme Court judgment made the Affordable Care Act's Medicaid expansion optional for states, the current period of differential Medicaid coverage will allow researchers to study a variety of questions related to access to care and health gains for the most vulnerable segments of the population.

"In the case of ESRD, we strongly recommend that detailed data also be collected concerning the intermediate markers or indicators, such as diabetes and hypertension control, to understand the nature of the impact of the provision of expanded coverage," wrote Mehrotra and Kessler.

The article, entitled "State Medicaid Coverage, ESRD Incidence, and Access to Care," is online at http://jasn.asnjournals.org/.

The editorial, entitled "Health Insurance, Access to Care, and ESRD: An Intricate Web," is online at http://jasn.asnjournals.org/.

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KidneyNews

ASN Kidney News is published by the American Society of Nephrology
1510 H Street NW, Suite 800, Washington, DC 20005. Phone: 202-640-4660

www.asn-online.org

Postmaster: Please send address changes to *ASN Kidney News*, c/o Customer Service, American Society of Nephrology 1510 H Street NW, Suite 800, Washington, DC 20005.

Publications mail agreement No. 40624074. Return undeliverable Canadian addresses to PO Box 503, RPO West Beaver Creek, Richmond Hill ON L4B 4R6

ASN Kidney News (ISSN print 1943-8044 and online 1943-8052) is an official publication of the American Society of Nephrology, 1510 H Street NW #800, Washington DC 20005, and is published monthly. Periodicals postage paid at Washington, DC and at additional mailing offices. Subscription rates: $12 per year. To order, please email bhenkel@asn-online.org. Subscription prices subject to change. Annual ASN membership dues include $12 for *ASN Kidney News* subscription.

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Corporate Supporters

The ASN Corporate Support Program recognizes supporters year round for their generous contributions to the Society. Through this program, supporters help ASN lead the fight against kidney disease. ASN gratefully acknowledges the following companies for their contributions in 2013.

Diamond Level

abbvie

ALEXION

AMGEN

FRESENIUS MEDICAL CARE

Otsuka
Otsuka America Pharmaceutical, Inc.

QUESTCOR PHARMACEUTICALS, INC.

SANOFI

Platinum Level

KERYX BIOPHARMACEUTICALS, INC

Glomerular Disease

Advancing Understanding and Treatment of Glomerular Disease

By Richard A. Lafayette

Primary glomerular disease is an important cause of chronic and end stage renal disease

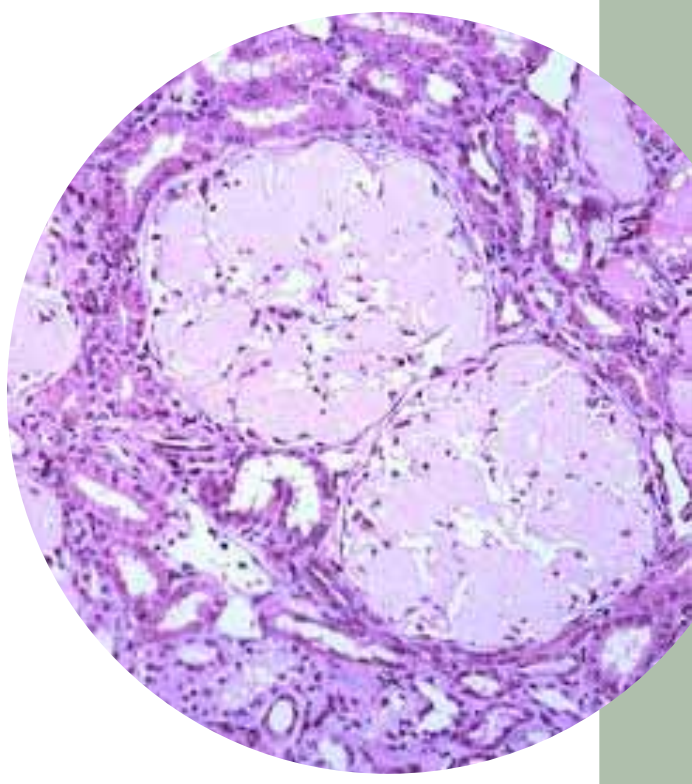
Chronic kidney disease (CKD) is increasingly recognized as a growing global challenge, affecting up to 16 percent of the adult population (1,2). Although the veritable explosion in type II diabetes is largely responsible for this growth in developed and many developing countries, primary glomerular disease continues to contribute meaningfully to the CKD epidemic (2). These diseases account for roughly 10 percent of CKD cases in the United States and up to 50 percent in other countries (3, 4). Primary glomerular diseases contribute to considerable morbidity, cost, and mortality. As part of this, they contribute importantly to ESRD in the United States (Figure 1). More than 80,000 patients with ESRD report glomerulonephritis as their primary cause of ESRD, and 9000 patients with primary glomerular disease begin undergoing dialysis each year (2). In addition to the burden of glomerular disease in adults, it is noteworthy that roughly one in four cases of pediatric ESRD is related to primary glomerular disease (2).

Recent discoveries have focused attention on primary glomerular disease

Whereas many speak of limited progress in the field of glomerulonephritis, and being stuck with treatments similar to those we used decades ago, recent discoveries and trials suggest that advances are indeed being made and are likely to be extended. Minimal change disease (MCD), focal segmental glomerular sclerosis (FSGS), membranous nephropathy (MN), and IgA nephropathy (IgAN) cause proteinuria by means of glomerular podocyte injury, most likely related to immune dysregulation, although the exact mechanisms are still unknown (3,4). For populations at risk, the mechanisms of podocyte-related and non–podocyte-related injury, clinical manifestations (including impaired renal function, hematuria, proteinuria, and hypertension), response to corticosteroids and other anti-inflammatory and immunosuppressive therapies, and rates of progression to ESRD differ widely among these diseases. Still, all these conditions have common features that link them together. New insights into their mechanisms are most likely to lead to inroads into prevention and therapy. Genetic mutations that lead to syndromes of podocyte dysfunction and injury have yielded conditions indistinguishable from classic MCD and FSGS (5,6). New findings derived from linkage analyses may elucidate other glomerular diseases such as MN, FSGS, or IgAN (7,8). Defects in specific proteins, such as angiopoetin-like 4 protein, may also lead to MCD, and these defective proteins may be specific targets of therapy (9). Specific antibodies have been linked to certain disease states, such as antibodies to galactose-deficient IgA1 in IgAN and antibodies to the M-type phospholipase A2 in MN (10,11). Increased levels of circulating factors such as soluble urokinase-type plasminogen activator receptor have been reported in FSGS and initially appeared to be related to the degree of impaired kidney function (12). These selected examples demonstrate that distinct pathways may be examined in these patients to help define the mechanisms of disease, and these approaches may result in the discovery of biomarkers of the specific disease, prognostic indicators, or novel targets for therapy.

Insights into advances in glomerular disease

Building on these findings, this issue of *Kidney News* presents some insights and opinions regarding glomerular diseases, ranging from specific discoveries through mechanisms of collaborative studies and proceeding to suggestions about how to further improve the care of patients with glomerular disease, whether primary or secondary to systemic disease. It is hoped that these efforts will usher in more interest, resources, and effort in the area to ultimately benefit the patients we serve.

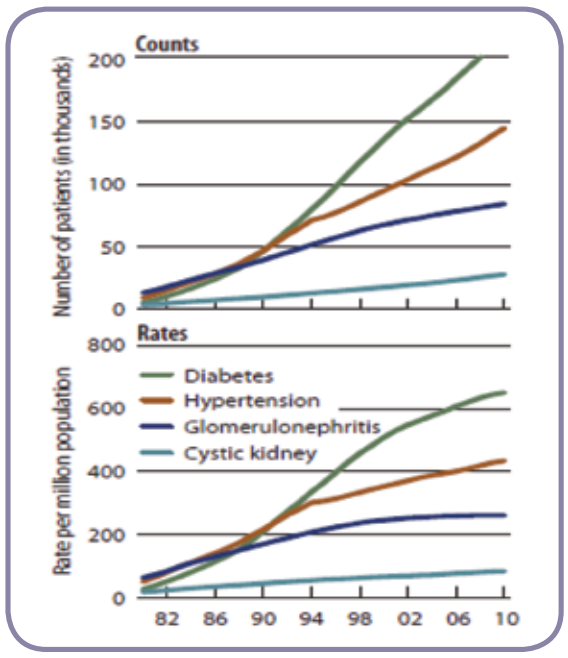


References

1. US Renal Data System. USRDS 2012 Annual Data Report. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2012.
2. El-Nahas AM, Bello AK. Chronic kidney disease: the global challenge. *Lancet* 2005; 365:331–340.
3. Couser WG. Mediation of glomerulonephritis: basic and translational concepts. *J Am Soc Nephrol* 2012; 23:381–399.
4. Rovin BH, Schreiner GF. Cell mediated immuity in glomerular disease. *Ann Rev Med* 1991; 42:25–33.
5. Pollak MR. The genetic basis of FSGS and steroid-resistant nephrosis. *Semin Nephrol* 2003; 23:141–146.
6. Liu Z, et. al. Alpha-actinin-4 and CLP36 protein deficiencies contribute to podocyte defects in multiple human glomerulopathies. *J Biol Chem* 2011; 286:30795–30801.
7. Gharavi AG, et al. Genome-wide association study identifies susceptibility loci for IgA nephropathy. *Nat Genet* 2011; 43:321–327.
8. Stanescu HC, et al. Risk HLA-DQA1 and PLA(2)R1 alleles in idiopathic membranous nephropathy. *N Engl J Med* 2011; 364:616–626.
9. Berthoux F, et al. Autoantibodies targeting galactose-deficient IgA1 associate with progression of IgA nephropathy. *J Am Soc Nephrol* 2012; 9:1579–1587.
10. Beck LH Jr., et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med* 2009; 361:11–21.
11. Clement LC, et al. Podocyte secreted angiopoietin-like 4 mediates proteinuria in glucocorticoid sensitive nephrotic syndrome. *Nat Med* 2011; 17:117–123.
12. Wei C, et al. Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis. *Nat Med* 2011; 17:952–960.

Richard A. Lafayette, MD, FACP, is associate professor of medicine in the Division of Nephrology at Stanford University School of Medicine in Palo Alto, CA. Dr. Lafayette edited this special section for ASN Kidney News.

Figure 1. US Renal Data System data for prevalence of glomerulonephritis as a cause of ESRD.



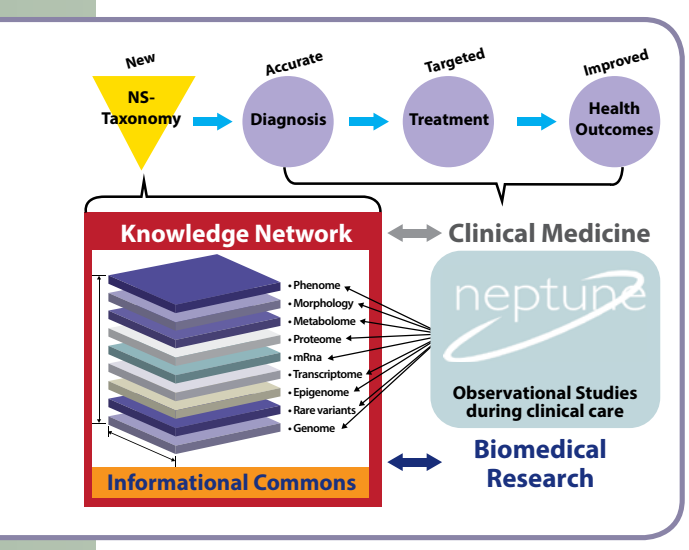
The Nephrotic Syndrome Study Network: A Rare Disease Network for Precision Medicine in Nephrotic Syndrome

By John Sedor, Matthias Kretzler, and Denise L. Taylor-Moon

The main goal of the Nephrotic Syndrome Study Network, NEPTUNE, is to build a translational research infrastructure for diseases manifesting as nephrotic syndrome (NS), which includes focal and segmental glomerulosclerosis (FSGS), minimal change disease (MCD), and membranous nephropathy (MN) (1). The network of investigators from 21 academic centers across the United States and Canada, and two patient interest groups, the NephCure Foundation and the Halpin Foundation, have worked closely together to study these rare glomerular diseases. Despite their rarity, these diseases generate enormous individual, societal, and economic burdens. The current classification of NS fails to capture the molecular bases of these diseases and consequently does not adequately predict either their natural history or their response to therapy. Given our limited understanding of MCD, FSGS, and MN biology and our inadequate classification system, it is not surprising that our therapeutic approach to these diseases is also imperfect. No new therapeutic targets have been validated by clinical trials for two decades, and current therapies rely almost exclusively on immunosuppression, which is used without a clear biological basis, is often not beneficial, and is frequently complicated by significant toxicities (2).

Given these shortcomings, basic science, translational, and clinical studies are needed that address the serious obstacles to providing effective care for the MCD, FSGS, or MN patient. NEPTUNE was funded in 2009 as part of the Rare Disease Clinical Research Networks with support from the National Institutes of Health and the NephCure Foundation to overcome the major barriers impeding the design of NS clinical trials. NEPTUNE is implementing the concept of precision medicine proposed by the Institute of Medicine in 2011 (3) (Figure 1). Precision medicine aims for the development of new disease definitions to be informed by a comprehensive, multilayered analysis of the disease course in observational cohort studies. NEPTUNE is recruiting a core cohort of patients with NS and has generated datasets, which define the underlying genetic architecture and capture environmental exposures, unique molecular phenotypes, histopathology, and prospective clinical outcomes. This disease knowledge along the genotype–phenotype continuum is used by basic and clinical scientists to develop a knowledge network of NS that defines the diseases from molecular pathogenesis rather than from histopathologic patterns. The molecular disease definition (i.e., taxonomy) will allow more accurate diagnosis, which is a prerequisite for targeted treatments that improve health outcomes in NS (Figure 1).

Figure 1. Precision medicine in nephrotic syndrome (mod. National Research Council, 2011).



The NEPTUNE cohort studies were designed to generate multilayered data on the disease course encompassing the genotype–phenotype continuum and generating a NS informational commons as requested by the national academies (1). NEPTUNE has assembled to date more than 450 NS participants with biosamples for the generation of individual catalogues of genomewide variation based on whole genome sequences, renal biopsy sample–derived tissue transcriptomes, and urine and plasma proteomes. These datasets are augmented with digital histopathologic information from renal biopsy specimens (4), longitudinal clinical phenotypes, and patient-reported outcomes, which in aggregate will be used to develop the framework for discovering disease mechanisms, testing biomarkers, and designing trials that integrate outcomes important to patients. In parallel, NEPTUNE is developing innovative tools for collaborations in molecular medicine. A web-based data sharing and analysis platform (Nephromine, www.nephromine.org) will allow the scientific community to link biopsy sample–derived gene expression datasets with predefined clinical parameters. Additional approaches for collaborative data mining and analysis are developed with the aim to establish the informational commons in NS research around the comprehensive clinical and molecular information.

NEPTUNE has extensive pilot, ancillary, and training programs open to the international scientific community to leverage its samples and core data for additional projects that will expand the knowledge base in the NS informational commons. NEPTUNE has supported and is closely linked with parallel efforts in Europe, China, India, and sub-Saharan Africa. Together with its international partners, NEPTUNE has established a joint systems biology core for analyses across disciplines and continents. Additionally, NEPTUNE is facilitating investigator- and industry-led clinical trials of targeted treatments in NS from trial design to implementation, using its clinical research network for effective recruitment of rare glomerular disease (i.e., MENTOR [Membranous Nephropathy Trial of Rituximab] and DUET, clinical trials No. NCT01180036 and No. NCT01613118).

Over the past 4.5 years, NEPTUNE has developed an investigative infrastructure that has established an observational longitudinal cohort of more than 450 incident adult and pediatric patients, allowing for standardized collection of renal biopsy tissues, blood and urine, comprehensive patient history, associated clinical data, and standardized measures of psychosocial well-being. Ongoing recruitment will further grow this unique cohort, and interested patients can be referred to NEPTUNE centers (see https://rarediseasesnetwork.epi.usf.edu/NEPTUNE/centers/index.htm for recruitment centers and investigators). This resource is available to all interested research investigators through ancillary studies to benefit the advancement of care of patients with FSGS, MCD, and MN. It is already used in more than 30 approved ancillary studies ranging from methods development to phase II clinical trials. For further information on available datasets and access, see http://www.neptune-study.org/.

With the joint support and participation of patients, the patient interest group NephCure, clinicians, clinician scientists, and bench researchers from academia and industry, therapeutic targets are now identified and can effectively be moved through a translational research pipeline for evaluation in NS patients.

Please contact the NEPTUNE investigators at neptunearc@umich.edu if you are interested in using or contributing to NEPTUNE.

John Sedor, MD, is affiliated with the Kidney Disease Research Center, Case Western Reserve University, Cleveland, Ohio. Matthias Kretzler, MD, and Denise L. Taylor-Moon are affiliated with the division of nephrology at the University of Michigan Health System in Ann Arbor, Michigan.

References

1. Gadegbeku CA, et al. Design of the Nephrotic Syndrome Study Network (NEPTUNE) to evaluate primary glomerular nephropathy by a multidisciplinary approach. *Kidney Int* 2013; 83:750–756.
2. Meyers CM, Geanacopoulos M, Holzman LB, Salant DJ. Glomerular Disease Workshop. *J Am Soc Nephrol* 2005; 16:3472–3476.
3. The Committee on a Framework for Developing a New Taxonomy of Disease, Board on Life Sciences, Division on Earth and Life Studies, National Research Council of the National Academies. *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease.* Washington, DC: 2011.
4. Barisoni L, et al. Digital pathology evolution in the multicenter Nephrotic Syndrome Study Network (NEPTUNE) *Clin J Am Soc Nephrol* 2013; 8:1449–1459.

Understanding MPGN In the Native and Transplanted Kidney

By Sanjeev Sethi and Fernando C. Fervenza

Membranoproliferative glomerulonephritis (MPGN), also termed mesangiocapillary glomerulonephritis, is a diagnosis based on a glomerular injury pattern common to a heterogeneous group of diseases (1). MPGN is characterized by both an inflammatory (proliferative) and resolving (membrane) phase. Histologically, the proliferative phase is characterized by an increase in mesangial and endocapillary cellularity, and the resolving phase is characterized by an increase in mesangial matrix and capillary wall remodeling with basement membrane material forming a wall, resulting in double contour formation.

Previously, MPGN was classified into MPGN types I, II, and III, based on the ultrastructural location of the electron-dense deposits along the capillary walls. This classification did not take into account the underlying pathophysiology and was based purely on electron microscopic findings. However, a new Mayo classification of MPGN has recently been proposed that is based on the pathophysiology of MPGN (1,2). Immunofluorescence (IF) studies are the key to this classification, which now classifies MPGN into immune complex–mediated MPGN or complement-mediated MPGN (Figure 1). The basis of immune complex–mediated MPGN is the IF finding of mesangial and capillary wall Ig deposits with or without C3. Deposition of Ig activates the classic pathway of complement. As a result, C3 is often noted on IF studies along with the immune deposits. Furthermore, the type of immune deposits indicates the underlying cause. For example, deposition of monotypic Ig such as IgG-κ or IgM-λ indicates an underlying monoclonal gammopathy/dysproteinemia (3). By contrast, IgM deposits are often noted in chronic viral infections such as hepatitis C, whereas IgM-predominant deposits with smaller amounts of IgG are often noted in autoimmune diseases (4). Thus, immune complex–mediated MPGN typically results from one of three underlying disease mechanisms: monoclonal gammopathy/dysproteinemias, infections, or autoimmune diseases.

By contrast, complement-mediated MPGN results from glomerular deposition of C3 and other complement factors and degradation products (5). Deposition of C3 and complement factors results from dysregulation and overactivation of the alternative pathway of complement. The alternative pathway of complement is usually tightly regulated; however, dysregulation of the alternative pathway of complement can occur as a result of mutations/polymorphism (inherited) or autoantibodies (acquired) to complement regulating proteins, such as factor H, B, or I. In complement-mediated MPGN, the IF findings are characterized by dominant C3 staining with absent or scant Ig. The term C3 glomerulopathy is also used to define complement-mediated MPGN, inasmuch as other patterns in addition to the MPGN pattern, such as mesangial or diffuse proliferative glomerulonephritis, may be present. Electron microscopy further subdivides C3 glomerulopathy into C3 glomerulonephritis and dense deposit disease (DDD). In C3 glomerulonephritis, the deposits are discrete and are present in the mesangium and subendothelial region of the capillary walls and occasionally the intramembranous and subepithelial regions of the capillary walls as well. By contrast, in DDD the deposits are large, extremely dense (osmiophilic), and intramembranous, often resulting in marked thickening of the glomerular basement membranes.

It can be appreciated that the new Mayo classification attempts to elucidate the underlying causes of MPGN by dividing it into immune complex–mediated and complement-mediated disease. The classification facilitates appropriate evaluation, leading to identification of the correct cause. Treatment should then be based on the underlying pathogenesis of MPGN. Recent retrospective studies have tried to compare the course and prognosis between the two groups of MPGN. However, in fairness, one cannot adequately compare the two groups in retrospective studies because the underlying causes were poorly understood at the time, and none of the groups received specific treatment aimed at the cause.

The new Mayo classification of MPGN bears on the understanding of recurrence of MPGN after kidney transplantation. MPGN recurs in up to 50 to 70 percent of transplant recipients. Among the immune-complex MPGNs, recurrence rates are very high for MPGN resulting from monotypic Ig deposition from an underlying monoclonal gammopathy. Current recommendations include treatment of the monoclonal gammopathy before transplantation. By contrast, the recurrence rates of MPGN from infections and autoimmune disease are relatively low. With regard to complement-mediated MPGN, C3 glomerulonephritis recurs in almost two thirds of patients, with graft failure resulting in half of the patients within 6 to 7 years of recurrence (6). DDD also has a high rate of recurrence after kidney transplantation and results in graft failure in up to 50 percent of patients, with graft loss occurring within 2.5 years of transplantation.

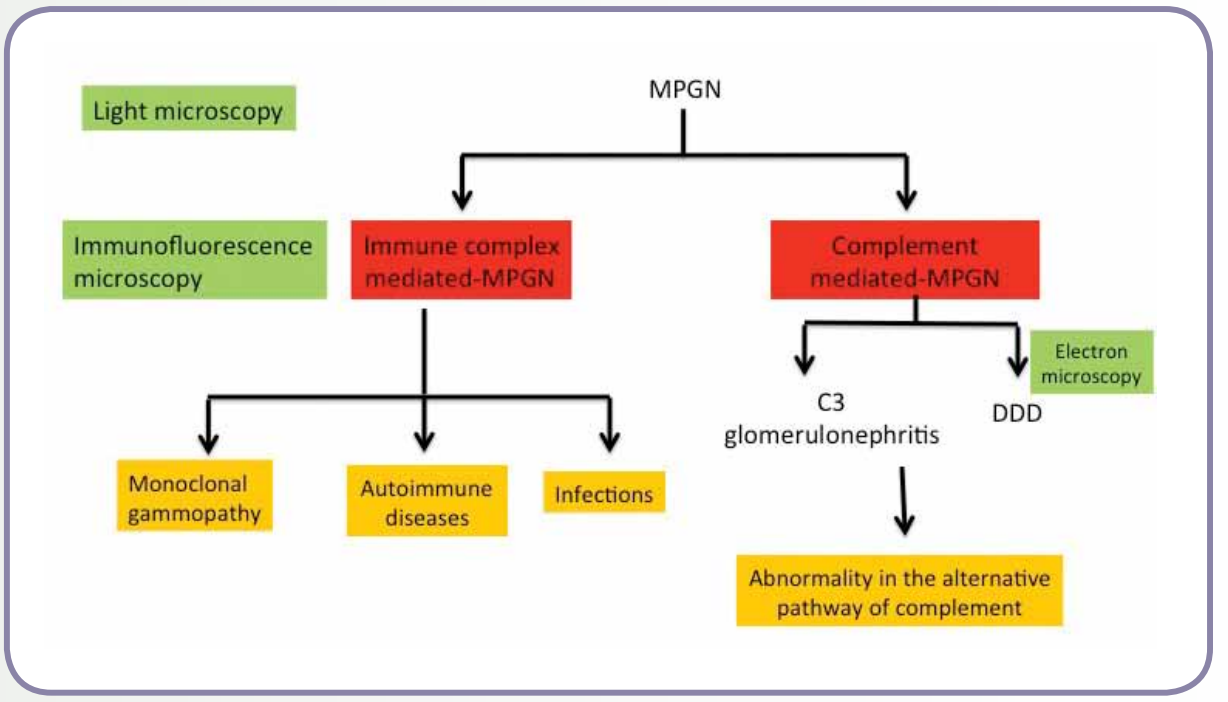
To summarize, the new Mayo classification of MPGN is easy to understand, is based on the underlying pathophysiology, and divides MPGN into immune complex–mediated MPGN and complement-mediated MPGN for further pathologic subheadings. The classification facilitates appropriate laboratory evaluation, leading to identification of the underlying cause of MPGN and the hope of better guidance for management.

Sanjeev Sethi and Fernando C. Fervenza are affiliated with the Mayo Clinic, Rochester, MN.

References

1. Sethi S, Fervenza FC. Membranoproliferative glomerulonephritis: a new look at an old entity. *N Engl J Med* 2012; 366:1119–1131.
2. Sethi S, Fervenza FC. Membranoproliferative glomerulonephritis: pathogenetic heterogeneity and proposal for a new classification. *Semin Nephrol* 2011; 31:341–348.
3. Sethi S, et al. Membranoproliferative glomerulonephritis secondary to monoclonal gammopathy. *Clin J Am Soc Nephro*l 2010; 5:770–782.
4. Zand L, et al. Membranoproliferative glomerulonephritis associated with autoimmune diseases. *J Nephrol* 2014; 27:165–171.
5. Sethi S, et al. C3 glomerulonephritis: clinicopathological findings, complement abnormalities, glomerular proteomic profile, treatment, and follow-up. *Kidney Int* 2012; 82:465–473.
6. Zand L, et al. Clinical findings, pathology, and outcomes of C3GN after kidney transplantation. *J Am Soc Nephrol* 2013 Dec 19 [Epub ahead of print].

Figure 1. **Proposed classification scheme for MPGN into immune complex–mediated and complement-mediated MPGN, based on immunofluorescence microscopy (IF) findings. Immune complex–mediated MPGN is characterized by the presence of immunoglobulins (Ig) and/or C3, while complement-mediated MPGN is characterized by the presence of bright C3 and absent/scant Ig. Evaluation of immune complex–mediated MPGN should include work-up for monoclonal gammopathy, autoimmune diseases, and infections. On the other hand, evaluation of complement-mediated MPGN should include work-up for functional, acquired, and inherited abnormalities of the alternative pathway of complement.**



Progress in IgA Nephropathy and Its Clinical Implications

By Pietro A. Canetta

In the past several years, major progress has been made in understanding the mechanisms underlying the development and progression of IgA nephropathy (IgAN). These advances have contributed to the generation of an ever-expanding catalog of measurable variables that provide diagnostic or prognostic information about IgAN. Such measures span the gamut from immune mediators and metabolites detectable in serum or urine, to genetic and epigenetic traits, to histologic features both traditional and novel. IgAN has a complex multistep pathogenesis involving essentially every branch of the immune system, and this progress in measurable variables holds great promise for better characterizing the disease and, in turn, allowing for a more nuanced approach to prognosis and therapy.

The modern understanding of IgAN pathogenesis centers on the creation and deposition of IgA-containing immune complexes in the glomerular mesangium (Figure 1) (1).The earliest step appears to be the development of elevated circulating levels of poorly glycosylated immunoglobulin A1, known as galactose-deficient IgA (Gd-IgA1). This alone is insufficient to cause disease because elevated Gd-IgA1 levels are also found in healthy relatives of IgAN patients. Next, either IgA or IgG antibodies are formed that bind to Gd-IgA1, leading to the development of immune complexes. There are many hypothesized triggers for this autoantibody production, but a common theme is activation of mucosal immunity, especially in the tonsillar or intestinal lymphoid tissue. As immune complexes form or are deposited in the renal mesangium they activate local inflammatory cascades whose final common pathway is cell proliferation, matrix production, and eventually glomerular sclerosis and interstitial fibrosis. In this final stage of pathogenesis, IgAN becomes clinically apparent, with hematuria, proteinuria, and eventual loss of glomerular filtration.

Two key measurable elements of the pathogenic mechanism are circulating Gd-IgA1 and the antiglycan autoantibodies. Studies have separately demonstrated that both elevated Gd-IgA1 levels and elevated antiglycan levels predict an increased risk for kidney failure, and at least one study of longitudinal measurements has directly correlated the level of these biomarkers with disease activity (2). Validation of these findings and the development of reliable, affordable, and commercially available assays could provide a much needed biomarker of immune activity, perhaps akin (and hopefully superior) to DNA antibodies in systemic lupus erythematosus or ANCA levels in pauci-immune glomerulonephritis. This would represent a major advance in the clinical approach to IgAN, supplementing the current time-tested but entirely nonspecific standards of disease activity, proteinuria, and serum creatinine.

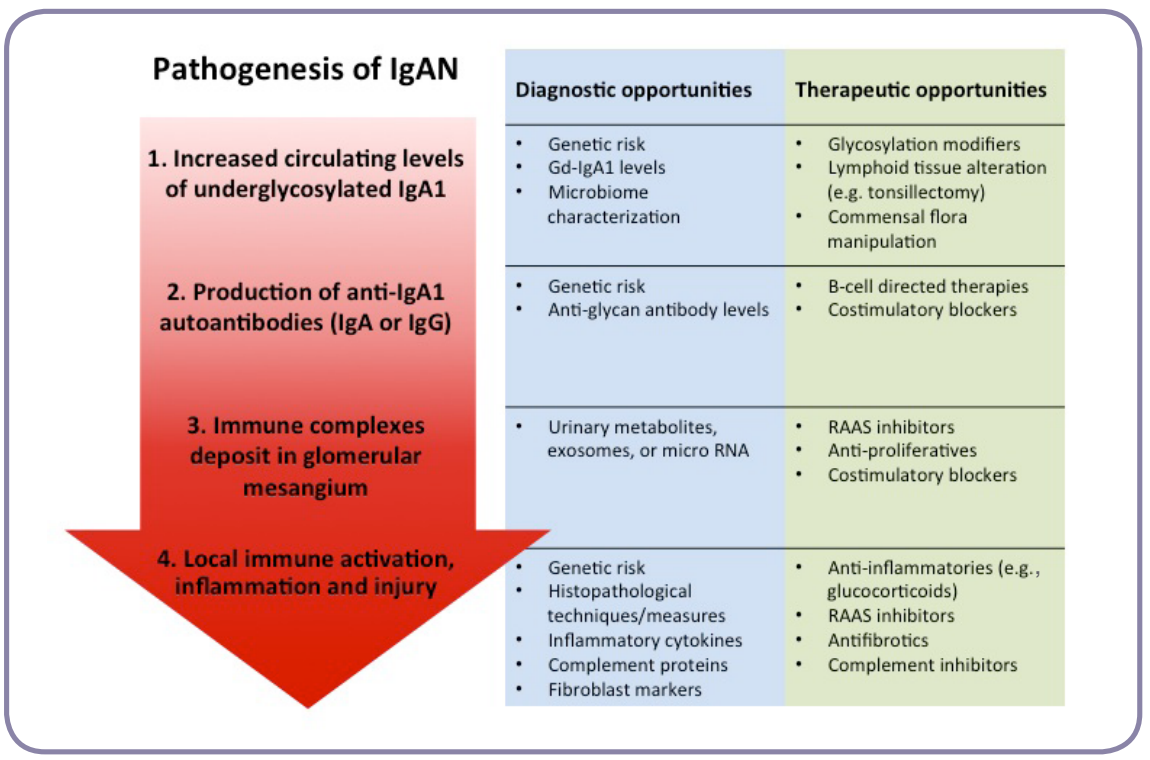
Because kidney biopsy remains the gold standard for IgAN diagnosis and an invaluable source of prognostic information, efforts continue to refine and augment the information gleaned from histopathology. A major advance was the development and publication of the Oxford classification of IgAN in 2009, involving four easily identified variables that were shown to predict clinical outcome in the inception cohort and to be reproducible among pathologists: mesangial cellularity (M), endocapillary proliferation (E), segmental sclerosis (S), and tubular atrophy/interstitial fibrosis (T) (3). Subsequent to the publication of the Oxford classification, many reports have evaluated it in various cohorts. The largest was the recent publication from the pan-European VALIGA study, which confirms and generalizes the value of Oxford across a widely diverse group of patients representing the entire (European) spectrum of IgAN patients undergoing biopsy (4). VALIGA and several other studies have identified the "E" component as the least predictive of prognosis, but this interpretation is confounded because of the diffusion (expanded use) of immunosuppressive treatment for IgAN, whereby "E" may indicate disease amenable to therapy rather than irreversible damage like fibrosis. Beyond traditional biopsy techniques, studies continue to identify novel histopathologic markers of prognosis in IgAN, including specific immune cells, complement components, and markers of inflammation or fibrosis. Although the majority are unlikely to become routine in practice, they inform our understanding of disease pathogenesis, and they identify potential therapeutic targets.

Among the most illuminating developments in IgAN is the increasingly thorough characterization of the genetic contributions to both disease establishment and severity. Although geographic and racial differences in disease prevalence have long been recognized, until recently it was still debated to what degree these were due to differences in disease ascertainment (e.g., due to diverse local biopsy practices) rather than biology. It is now clear that a substantial portion of disease risk is conferred genetically.

Within the past 5 years, a series of genomewide association studies have identified at least seven susceptibility loci for IgAN (5). Furthermore, in an elegant example of congruity between genetics and epidemiology, a comprehensive geospatial analysis of genetic risk led by colleagues at Columbia University demonstrated that changes in genetic risk closely paralleled disease prevalence across 85 populations worldwide (5). The genetic loci identified thus far comprise genes associated with innate immunity, adaptive immunity (with the strongest signals consistently seen in the *MHC* region), and the complement system. This last locus is particularly interesting, involving genes encoding complement factor H and its five related proteins (*CFHR1-5*), which regulate the alternative complement pathway. Mutations in the *CFH/CFHR* gene region have been associated with C3 glomerulopathy, raising the intriguing possibility of overlapping pathogenic mechanisms with this much rarer form of proliferative glomerulonephritis. Although complement activation is well recognized in IgAN, the relative importance of the different initiating pathways—classic, alternative, and lectin—remains unclear. A series of reports has demonstrated the prognostic significance of various complement components on biopsy, including mannose-binding lectin, C1q, C4d, C3a, and C5a, and both mesangial and serum C3. These indicate that complement activation in IgAN may be a promising target for therapy.

What developments in IgAN can we expect in the near future? First, the number of genetic loci associated with the disease will undoubtedly expand as results from larger and higher-resolution genomewide studies are published. Large-scale,

Figure 1. Left, stepwise schematic of the pathogenesis of IgAN. Adjacent to each step are listed relevant opportunities for diagnosis or therapy. RAAS, renin-angiotensin aldosterone system.



longitudinal cohort studies are needed to validate proposed biomarkers and discover new ones; one notable example is the CureGN study, recently funded by the National Institutes of Health, an ambitious undertaking that will enroll patients with various glomerular diseases, including 600 patients with IgAN. The results from ongoing randomized controlled treatment trials are eagerly awaited, in particular the nearly completed German STOP-IgAN study, which examines the effects of immunosuppression versus supportive care, stratified by estimated GFR. Finally, we can expect to see novel immunosuppressive approaches tested in patients, targeting pathways across the disease pathogenesis including B-cell immunity, antibody generation, complement activation, inflammation, and fibrosis (Figure 1). Given the progress achieved thus far, both nephrologists and their patients have ample reason to be excited.

Pietro A. Canetta, MD, is assistant professor of medicine, division of nephrology, Columbia University College of Physicians and Surgeons, New York.

References

1. Mestecky J, et al. IgA nephropathy: molecular mechanisms of the disease. *Annu Rev Pathol* 2013; 8:217–240.
2. Suzuki Y, et al. Serum levels of galactose-deficient immunoglobulin (Ig) A1 and related immune complex are associated with disease activity of IgA nephropathy. *Clin Exp Nephrol* 2014 Jan 30 [Epub ahead of print].
3. Cattran DC, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. *Kidney Int* 2009; 76:534–545.
4. Coppo R, et al. Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments. *Kidney Int* 2014 Apr 2 [Epub ahead of print].
5. Kiryluk K, et al. Pathogenesis of immunoglobulin A nephropathy: recent insight from genetic studies. *Annu Rev Med* 2013; 64:339–356.
6. Kiryluk K, et al. Geographic differences in genetic susceptibility to IgA nephropathy: GWAS replication study and geospatial risk analysis. *PLoS Genet* 2012; 8:e1002765.

New Treatments for Idiopathic Membranous Nephropathy

By Claudio Ponticelli

The treatment of idiopathic membranous nephropathy (IMN) has been a matter of discussion for many years. Given the variable clinical course and potential toxicity of current regimens, the main issue nephrologists face at the moment are who to treat and with what regimen. Conservative management is justified for patients with subnephrotic proteinuria, inasmuch as spontaneous remission occurs more frequently in these patients, and their long-term prognosis is usually excellent.

By contrast, patients with nephrotic syndrome (NS) may show a progression to ESRD and are more frequently affected by any of several extrarenal complications. Thus, initiation of specific therapy is indicated for patients with declining renal function or full-blown NS (1). The guidelines of Kidney Disease: Improving Global Outcome (KDIGO) recommend a 6-month course of alternating monthly cycles of oral and intravenous corticosteroids, and oral alkylating agents. The continuous use of alkylating agents may also be effective but is associated with a greater risk of severe adverse events. Cyclosporine or tacrolimus have been suggested as alternative options in nonresponders or in patients who do not tolerate treatment with steroids and cytotoxic drugs (2).

In the past few years, the discovery that most patients with IMN have circulating antibodies directed against the M-type phospholipase A2 receptor provided important insights into the mechanistic interpretation of IMN (3). Further studies confirmed that this receptor represents the main antigen involved, although other podocyte antigens may also play a role in the pathogenesis of this disease.

In the same period of time, new drugs have been used for IMN, three of which show a potential beneficial effect: mycophenolate mofetil (MMF), adrenocorticotropic hormone (ACTH), and rituximab.

Mycophenolate mofetil

Retrospective studies and three small randomized controlled trials (RCTs) evaluated the effects of MMF in IMN. Only a small rate of remission was reported by observational studies when MMF was used as monotherapy, and negative results were reported by a French trial. That trial randomized 36 patients to either MMF alone (2 g per day for 12 months) or symptomatic therapy, and the rates of remission were similar (4). Still, a response in about two-thirds of patients (predominantly partial remission) was reported by a retrospective study in which MMF was combined with oral prednisone and methylprednisolone pulses. However, patients with NS frequently experienced relapse after treatment was interrupted (5). Two small RCTs with short-term follow-up reported remissions in about 70 percent of patients treated with MMF and steroids—a rate similar to that observed in patients assigned to a steroid/cytotoxic drug regimen (6, 7).

These data are insufficient to enable any firm conclusion to be drawn. Trials with adequate sample size and follow-up are needed to better clarify the efficacy and safety of MMF with corticosteroids in IMN. At present, this therapy may be considered for patients who do not respond to other treatments. To prevent relapses, this therapy should be given for at least 1 year if well tolerated.

Adrenocorticotropic hormone

Berg et al. (8) first showed that prolonged administration of synthetic ACTH (Synacthen) could obtain remission in patients with IMN and NS. A small RCT compared a 12-month course of Synacthen, 1 mg twice a week for 1 year, with a 6-month regimen based on steroids alternated with a cytotoxic drug every month. After a mean follow-up time of 23 months, no difference in the rate of remission or in the mean decline in proteinuria was seen between the groups (9). In an observational study, natural ACTH (Acthar gel), given at a dose of 80 units subcutaneously twice a week for 6 months, was used in 11 patients with IMN and NS. Three complete remissions and six partial remissions were observed (10). No relevant side effects have been reported in patients treated with synthetic or natural ACTH, but it should be taken into account that prolonged treatment may be complicated by diabetes, osteoporosis, or hypertension.

The available small studies suggest a potential role for ACTH in IMN. Yet, synthetic ACTH is no longer commercially available, whereas natural ACTH is burdened by an excessively high cost. Given that the mechanism of action of ACTH is related to the stimulation of melanocortin receptors (11), it is possible that less expensive and more specific synthetic melanocortin receptor agonists will be developed in the near future.

Rituximab

Recently, Ruggenenti et al. (12) reported their cumulative experience with rituximab in 100 patients with MN. After a mean follow-up time of 29 months, 27 patients showed complete remission and 38 partial remission, the median time to response being around 7 months. The response to treatment did not change whether rituximab was used in treatment-naïve patients or in patients previously treated with ineffective regimens. No severe side effects were reported. However, 4 patients died, cancer developed in 3, and progression to ESRD occurred in 4. The authors attributed these events to previous treatment, but a direct or indirect role of rituximab cannot be excluded. Good results have also been reported in other observational studies. In a multicenter study of 20 patients treated with four weekly courses of rituximab repeated after 6 months, 2 patients did not respond, 4 entered complete remission, 12 underwent partial remission, 1 patient had limited response, and 1 experienced relapse. No severe adverse events were reported (13).

From the available reports it can be extrapolated that 65 percent to 80 percent of patients may have a complete or partial (more frequent) response to rituximab. However, apart from the high cost, the optimal dose, timing, and duration of re-treatment and the long-term benefit-to-harm ratio of rituximab remain incompletely explored. It is also unclear whether patients with renal dysfunction, tubulointerstitial lesions, or both will be sensitive or resistant to such treatment.

Summary and conclusions

At present, there are at least five different options for treating nephrotic patients with IMN. Therapies based on cycling cytotoxic agents/steroid administration or calcineurin inhibitors have been tested by RCTs, meta-analyses, and retrospective clinical studies to assess their effectiveness and safety profile. It is more difficult to determine the role of new treatments in IMN in the absence of rigorous studies and long-term follow-up times.

MMF associated with corticosteroids might be an alternative therapy in patients with contraindications or poor response to cytotoxic therapy. However, solid studies are required to confirm the efficacy of this association and to indicate the optimal dosage and duration of therapy.

The mechanism of action of ACTH is completely different from that of immunosuppressive agents. Only a few small studies have been conducted with ACTH. The results are interesting, but Synacthen has been retired, and the exceedingly high cost of gel ACTH may impede further development of this treatment in IMN.

The results with rituximab are impressive. However, as discussed above, more answers are needed. Trials comparing the efficacy and toxicity of rituximab with regimens based on cytotoxic/steroid administration will be welcome. The decision on whom, when, and how to treat is completely up to each clinician. However, it should be kept in mind that whatever the treatment, an early response is seldom observed. In many cases, remission can develop months or even years after the therapy has been completed.

Claudio Ponticelli is associated with the Humanitas Clinical and Research Center, Milano, Italy.

References

1. Ponticelli C, Glassock RJ. Glomerular diseases: membranous nephropathy—a modern view. *Clin J Am Soc Nephrol* 2014; 9:609–616.
2. Radhakrishnan J, Cattran DC. The KDIGO clinical practice guideline on glomerulonephritis: reading (guide)lines—application to the individual patient. *Kidney Int* 2012; 82(2):840–856.
3. Beck LH Jr, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med* 2009; 361:11–21.
4. Dussol B, et al. Mycophenolate mofetil monotherapy in membranous nephropathy: a 1-year randomized controlled trial. *Am J Kidney Dis* 2008; 52:699–705.
5. Branten AJ, et al. Mycophenolate mofetil in idiopathic membranous nephropathy: a clinical trial with comparison to a historic control group treated with cyclophosphamide. *Am J Kidney Dis* 2007; 50:248–256.
6. Chan TM, et al. Prospective controlled study on mycophenolate mofetil and prednisolone in the treatment of membranous nephropathy with nephrotic syndrome. *Nephrology* (Carlton) 2007; 12:576–581.
7. Senthil Nayagam L, et al. Mycophenolate mofetil or standard therapy for membranous nephropathy and focal segmental glomerulosclerosis: a pilot study. *Nephrol Dial Transplant* 2008; 23:1926–1930.
8. Berg AL, et al. Beneficial effects of ACTH on the serum lipoprotein profile and glomerular function in patients with membranous nephropathy. *Kidney Int* 1999; 56:1534–1543.

9. Ponticelli C, et al. A randomized pilot trial comparing methylprednisolone plus a cytotoxic agent versus synthetic adrenocorticotropic hormone in idiopathic membranous nephropathy. *Am J Kidney Dis* 2006; 47:233–240.
10. Bomback AS, et al. Treatment of nephrotic syndrome with adrenocorticotropic hormone (ACTH) gel. *Drug Des Devel Ther* 2011; 5:147–153.
11. Lindskog Jonsson A, et al. Effects of melanocortin 1 receptor agonists in experimental nephropathies. *PLoS One* 2014; 9:e87816.
12. Ruggenenti P, et al. Rituximab in idiopathic membranous nephropathy. *J Am Soc Nephrol* 2012; 23:1416–1425.
13. Fervenza FC, et al. Rituximab therapy in idiopathic membranous nephropathy: a 2-year study. *Clin J Am Soc Nephrol* 2010; 5:2188–2198.

Pregnancy in Women with Glomerular and other Chronic Kidney Disease and the Need for International Collaboration

By Ayodele Odutayo and Michelle Hladunewich

Patients with kidney disease are at increased maternal and fetal risk during pregnancy. In particular, glomerular-based kidney disease is overrepresented among younger patient populations and is therefore a common form of kidney disease that requires management during pregnancy. Potential untoward outcomes include progression of underlying renal dysfunction, worsening of urine protein excretion and hypertension, and untoward fetal outcomes including intrauterine growth restriction and preterm delivery. However, prognostication of an individual woman's pregnancy-associated risk in the setting of chronic kidney disease (CKD) remains profoundly challenging, especially in the context of glomerular-based kidney disease, wherein there is often a combination of different degrees of renal insufficiency, proteinuria, and hypertension. Most studies to date are too small to account for the potential differential impact of these important factors on pregnancy outcome, leaving the clinician to approximate risk for one of a young woman's most important life decisions, wherein a bad outcome can have a profound impact on both her long-term health and that of her child. Because the literature provides limited guidance, divergent opinions arise with respect to the impact of kidney disease on future CKD progression and on pregnancy outcomes.

Early studies generally used serum creatinine level to stratify pregnancy risk based on the following thresholds: mild (≤123 μmol/L [1.4 mg/dL]), moderate (124–220 μmol/L [1.4 to <2.5 mg/dL]) and severe (≥220 μmol/L [2.5 mg/dL]) renal insufficiency. It has been well in excess of a decade since Jones and Hayslett published their classic report in the *New England Journal of Medicine* noting that women with advanced stages of CKD are at risk for loss of kidney function and compromised pregnancy outcomes (1). In this report of 67 women and 82 pregnancies, pregnancy-related loss of kidney function was noted in 43 percent of pregnancies, with 10 percent of women rapidly experiencing progression toward ESRD. Of interest, not all the accelerated loss occurred in patients with the most severe renal compromise, inasmuch as progression to ESRD was also noted in 3 of 9 patients with moderate renal insufficiency—a proportion similar to that in the severe renal insufficiency group. A significant limitation of this study was its reliance on serum creatinine as a marker of renal function, which is too imprecise to stratify women before pregnancy because it does not take into account patient size and muscle mass. Furthermore, in young women, serum creatinine is often inadequately reflective of the actual degree of histologic renal damage. Finally, no adjustments were made for either the degree of urine protein or the presence of hypertension.

Subsequent studies have therefore used the Modification of Diet in Renal Disease formula to classify preconception renal insufficiency. In a more recent study, which excluded women with diabetes or lupus, 49 women with stage 3–5 CKD were divided into four groups based on preconception estimated GFR (eGFR) (≥40 or <40 mL/min/1.73 m^2) and proteinuria (≥1 or <1 g/24 h) (2). In women with eGFR 40 mL/min/1.73 m^2 or higher, there was no difference in the rate of eGFR decline up to 1 year after pregnancy, irrespective of preconception proteinuria. By contrast, among women with eGFR below 40 mL/min/1.73 m^2, the rate of eGFR decline was increased in those with proteinuria 1 g/24 h or higher (2). Although the findings that relate proteinuria and severe renal disease to reductions in eGFR confirm the earlier literature, the absence of any eGFR reduction in the ≥40 mL/min/1.73 m^2 group warrants further scrutiny because only 6 women were included in this group with more moderate disease. Furthermore, a recent study that stratified women using the Chronic Kidney Disease Epidemiology Collaboration equation demonstrated that more than 10 percent of patients with stage 2 CKD experienced at least a 25 percent increase in serum creatinine during pregnancy or shortly after delivery (3). Whether this change in renal function was transient was not clear from this study because follow-up data beyond 6 weeks postpartum were not provided.

With respect to fetal and maternal well-being, underlying kidney disease also predisposes to poor outcomes. In a large study of 640 women with stage 1 CKD with hypertension, the odds ratio for pre-eclampsia, small-for-gestational age, or preterm births was significantly elevated and increased with the degree of renal insufficiency (odds ratio = 10.09, 95 percent confidence interval 2.38–42.87, and odds ratio = 2.58, 95 percent confidence interval 1.40–4.75 in women with an eGFR of 60–74 and 75–89 mL/min, respectively) (4). Although microalbuminuria was not noted to increase the odds of the aforementioned maternal or fetal outcomes, none of the patients within this study had macroalbuminuria. As such, the effect of higher levels of urinary protein on pregnancy outcomes could not be examined. Finally, a recent meta-analysis of CKD and pregnancy demonstrated an overall risk of adverse maternal and fetal events that was at least fivefold and twofold higher, respectively, than in the general population (5). However, the poor methodologic quality of the studies included in the review was cited as a major limitation regarding this estimate (5).

Among the few definitive conclusions that can be made about CKD and pregnancy is that risk increases with the degree of renal dysfunction and is further heightened by comorbid conditions like hypertension. Typically, mild kidney disease (CKD stage 1) does not result in a progression of renal dysfunction, but it may still contribute to poor placental implantation and adverse maternal and fetal outcomes. Severe renal insufficiency (CKD stage 4–5), by contrast, frequently compromises maternal and fetal well-being. Pregnancy outcomes in the intermediate CKD stages require further clarification and disease-specific variations, accounting for different diseases, degrees of proteinuria, and even degrees of renal damage. Prior reports of lupus-associated and diabetic nephropathy having worse outcomes than other glomerular diseases should be tested. Because of the heterogeneity and poor methodologic quality of the existing literature, an overall risk estimate is currently difficult to generate. Well-designed studies with adequate numbers of participants are needed to clarify the pregnancy-associated risk faced by women with underlying CKD, and this is likely to require several centers working together to generate the information desperately required to assist the vast majority of young women with kidney disease in making adequately informed pregnancy decisions.

References

1. Jones DC, Hayslett JP. Outcome of pregnancy in women with moderate or severe renal insufficiency. *N Engl J Med* 1996; 335:226–232.
2. Imbasciati E, et al. Pregnancy in CKD stages 3 to 5: fetal and maternal outcomes. *Am J Kidney Dis* 2007; 49:753–762.
3. Alsuwaida A, et al. Impact of early chronic kidney disease on maternal and fetal outcomes of pregnancy. *J Matern Fetal Neonatal Med* 2011; 24:1432–1436.
4. Munkhaugen J, et al. Kidney function and future risk for adverse pregnancy outcomes: a population-based study from HUNT II, Norway. *Nephrol Dial Transplantat* 2009; 24:3744–3750.
5. Nevis IF, et al. Pregnancy outcomes in women with chronic kidney disease: a systematic review. *Clin J Am Soc Nephrol* 2011; 6:2587–2598.

Lupus Nephritis: The Case for Repeat Kidney Biopsy in the Management of Maintenance Therapy

By Brad H. Rovin and Samir V. Parikh

The therapy of proliferative lupus nephritis (LN) is generally divided into an initial phase of high-intensity immunosuppression to induce prompt clinical improvement, followed by a maintenance phase of lower-intensity immunosuppression to consolidate improvement into remission. Induction most often lasts 3 to 6 months, but maintenance lasts years and often indefinitely. The average duration of maintenance therapy in several recent randomized clinical trials was 3.5 years but ranged beyond 5 years. In fact, one of the most difficult management decisions in the care of LN patients is how long to continue maintenance immunosuppression. The most recent Kidney Disease Improving Global Outcomes (KDIGO) glomerulonephritis guidelines suggest continuing maintenance immunosuppression for at least 1 year beyond a complete renal response (1). However, this recommendation is not supported by randomized, prospective data, and no recommendations for withdrawal are given for a partial renal response. The 2012 LN guidelines sponsored by the American College of Rheumatology make no recommendations about the duration of maintenance immunosuppression (2), and the European League Against Rheumatism/European Renal Association-European Dialysis and Transplant Association guidelines suggest continuing maintenance therapy for at least 3 years (3).

Some insights into the duration of maintenance therapy can be derived from studies of repeat kidney biopsy in LN patients who have been treated with standard-of-care therapies. After 1.5 to 4.7 years of treatment, 30 to 77 percent of patients who underwent a repeated biopsy showed ongoing active proliferative LN or had undergone conversion to membranous LN, which also represents continued disease activity. Importantly, many of these patients had persistent substantial proteinuria, abnormal serum creatinine levels, or both. More worrisome are data showing that about one third of patients who had achieved complete clinical remission, and were clinically inactive for 2 years, still had histologic disease activity on repeat biopsy (4). These findings demonstrate that there can be discordance between the clinical metrics of renal response and histology. This discordance can also go in the other direction. A small study described several LN patients who had been aggressively treated but had persistent proteinuria (5). On repeat biopsy, these patients had no residual histologic activity and, barring sampling error, were complete responders histologically but not clinically (5).

We suggest that a repeat kidney biopsy could be a useful tool in guiding withdrawal of maintenance immunosuppression. For patients who have had a complete renal response, a biopsy before making the decision whether to taper off immunosuppression would identify patients who still have histologic activity and in whom it may be desirable to continue or even intensify immunosuppression. In the spirit of full disclosure, there have been no trials to test whether a patient who has achieved a complete clinical response, but still has some histologic activity on biopsy, will benefit from continuing or intensifying immunosuppression. For patients who have reached a partial remission and are in a stable condition for more than a year, a repeat biopsy could identify those who have achieved histologic remission and for whom tapering of immunosuppression may be considered.

Even if a kidney biopsy is used to inform a decision to taper off maintenance therapy, the question of when to perform the biopsy remains. This is difficult to answer on the basis of the available literature. At one extreme, some patients show no active lesions on biopsy specimens taken after induction therapy. It is conceivable that such patients could taper therapy at this point and avoid long-term maintenance immunosuppression. This rationale supports a role for repeat biopsy after the induction phase. However, tapering therapy after induction is not likely to become the prevailing consensus in the lupus community unless it is prospectively demonstrated to be safe. Most studies of repeat biopsy after LN induction therapy show improving histologic activity but not resolution of inflammation. An estimate of the minimal amount of time therapy is needed can be derived from existing studies of repeat biopsy. Several studies showed proliferative LN lesions in patients re-biopsied after 2 years of immunosuppressive therapy. One study found that 60 percent of patients who had achieved a complete renal response after 18 to 24 months of total treatment still had evidence of histologic activity in the kidneys (6). By contrast, after an average of 45 months of total therapy (minimal duration 42 months), only 30 percent of patients still had persistent activity on repeat biopsy (4). When these data are put together, a repeat kidney biopsy to inform the decision of whether to withdraw maintenance therapy could be considered after 3 to 3.5 years of total therapy (induction + maintenance) in clinically quiescent patients.

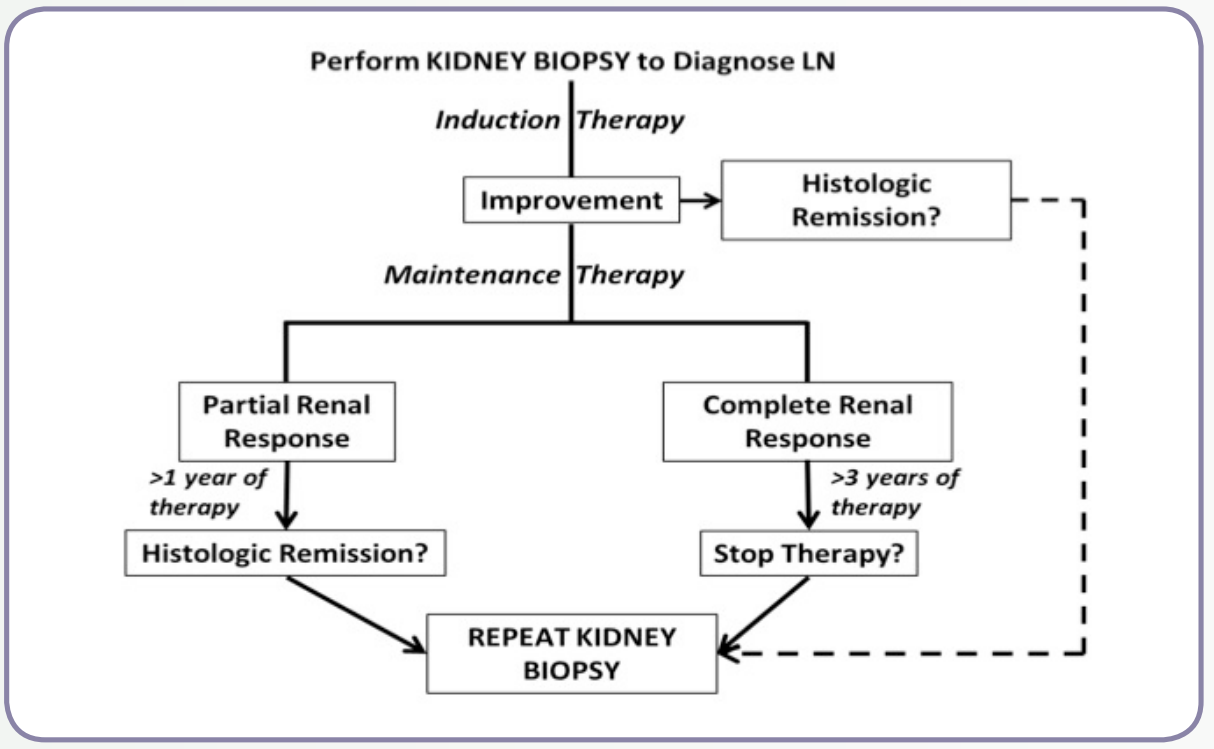
In summary, Figure 1 offers an algorithm for performing kidney biopsies in patients with LN to guide therapeutic choices. This algorithm has limitations because it is based on currently available data, most of which are neither prospective nor randomized. A study comparing renal outcomes in patients treated only on the basis of clinical data, or treated after consideration of clinical and repeat biopsy data, is needed to guide practice.

Brad H. Rovin, MD, FASN, is professor of medicine and pathology, division of nephrology, and vice chairman for research in the department of internal medicine, the Ohio State University Wexner Medical Center. Samir V. Parikh, MD, is assistant professor of medicine at the Ohio State University Wexner Medical Center.

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl* 2012; 2:221–232.
2. Hahn BH, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res* 2012; 64:797–808.
3. Bertsias GK, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. *Ann Rheum Dis* 2012; 71:1771–1782.
4. Alvarado A, et al. The value of repeat kidney biopsy in quiescent Argentinian lupus nephritis patients. *Lupus* 2014 Jan 8 [Epub ahead of print].
5. Condon MB, et al. Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids. *Ann Rheum Dis* 2013; 72:1280–1286.
6. Alsuwaida A, et al. Strategy for second kidney biopsy in patients with lupus nephritis. *Nephrol Dial Transplant* 2012; 27:1472–1478.

Figure 1. Algorithm for using the kidney biopsy to manage maintenance therapy of lupus nephritis. After the initial diagnostic biopsy, a repeated biopsy can be considered upon finishing induction therapy in patients who have completely responded. Some of these patients may be able to avoid prolonged treatment with immunosuppression, but this is not currently recommended. Most patients will be given maintenance immunosuppression after induction. Patients who achieve a complete renal response and have received more than 3 years of therapy are candidates for withdrawal of immunosuppression. This decision may be facilitated by a repeated biopsy to confirm histologic remission. Patients who do not achieve a complete clinical response, but have responded partially, may be considered for a repeat biopsy to determine whether they have attained a histologic remission. If so, and after a similar duration of total immunosuppressive therapy, such patients may be considered for withdrawal of maintenance therapy.



Policy Update

FDA: Labeling It Right Will Take a Community Effort

By Mark Lukaszewski

On April 1, 2013, the U.S. Food and Drug Administration (FDA) released its proposed rule for revision of nutrition and supplement labels (FDA 21 CFR Part 101).

The American Society of Nephrology, together with the National Kidney Foundation and 17 other organizations, developed a joint comment letter to the FDA regarding its proposed modifications (Table 1). The organizations agreed that most of the proposed changes have the potential to improve diets and overall health for millions of Americans. However, the letter focused not on what the FDA included in the proposed rule but rather on changes the agency omitted.

The proposed rule lists several important chronic diseases that constitute the leading causes of death and disability in the United States. But the FDA chose not to include chronic kidney disease on its list with other diseases like cardiovascular disease, cancer, obesity, and hypertension in its proposed rule. Given that kidney disease is the eighth leading cause of death in the United States—and that the kidney is critical in the metabolism and regulation of many nutrients in the human body—the FDA should give greater attention to this public health concern in this and other proposed rules, the letter argued.

The FDA made no mention of dietary phosphorus intake in the proposed rule, and the agency did not propose any changes with regard to how phosphorus content is reflected on the nutrition label.

"If FDA finalizes the proposed rule as is, it could be a significant missed opportunity to help people with kidney disease understand and better control their diet—and ultimately their health," said ASN President Sharon M. Moe, MD, FASN. The letter recommended that the FDA switch phosphorus content from voluntary to mandatory listing. The phosphate labeling could be further subdivided into natural content of phosphorus versus added phosphates, similar to a change that FDA proposed in this rule for distinguishing between natural sugar content of food versus added sugar.

Restricting dietary phosphorus intake is an important therapeutic strategy in patients with kidney disease. However, the increasing use of additives and the lack of mandatory labeling of phosphorus content pose significant—and often insurmountable—challenges to patients and their families who are trying to adhere to these important recommendations. In the United States, more than 45 percent of the best-selling grocery items contain phosphorus additives, and these items typically cost less and are eaten more often. Therefore, the search for foods that do not contain high amounts of phosphorus so they can maintain a healthful diet can make patients feel as if they are fighting an uphill battle.

ASN, NKF, and the other signing organizations hope that this joint letter will help the FDA recognize that diet management is critical in preventing progression of kidney disease and, for those whose kidneys have failed, that diet can have a monumental effect on maintaining the best possible quality of life.

These organizations will continue to advocate that the FDA include kidney disease on its list of chronic diseases and that the agency make the labeling of phosphorus content mandatory in the final rule.

The FDA's proposed rule states that when FDA is determining if mandatory versus voluntary labeling is indicated, "First we consider whether there is evidence of a relationship between the nutrient and a chronic disease, health-related condition, or health-related physiological endpoint. Second, we consider whether there is evidence of a problem related to health in the general U.S. population."

Table 1

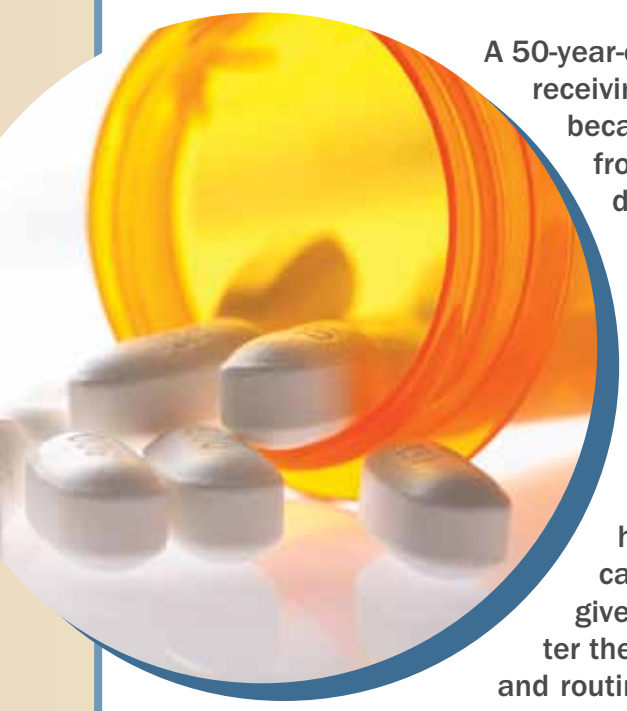
Organizations that signed comment letter to FDA

- Alport Syndrome Foundation
- American Association of Kidney Patients
- American Kidney Fund
- American Society of Nephrology
- American Nephrology Nurses Association
- American Renal Associates
- American Society for Apheresis
- American Society of Diagnostic and Interventional Nephrology
- American Society of Transplant Surgeons
- Dialysis Patient Citizens
- Home Dialyzors United
- The IgA Nephropathy Foundation of America
- National Kidney Foundation
- National Renal Administrators Association
- Nephrology Nursing Certification Commission
- Polycystic Kidney Disease Foundation
- Renal Physicians Association
- Renal Support Network

Practice Pointers

Drug Dosing in Chronic Kidney Disease and Dialysis: The Poison Is in the Dose

By Eugene C. Kovalik, for the American Society of Nephrology Practicing Nephrologists Advisory Group



A 50-year-old woman who had been receiving dialysis for many years because of complications from inflammatory bowel disease came to dialysis feeling "not quite right." Her thought processes felt muddled, and her movements were not "right," either. Upon further questioning, she stated that she had a shingles outbreak and had gone to an urgent care facility, where she was given full-dose acyclovir. After the medication was stopped and routine dialysis continued, her symptoms resolved.

When should providers begin to consider modifying drug dosing in patients with chronic kidney disease (CKD) and ESRD?

Once estimated GFR (eGFR) indicates stage 3 or higher CKD (<60 mL/min/1.73 m^2), modification of drug dose, of dosing intervals, or of both should be considered. This is particularly true if the medication has a significant renal clearance. Most laboratories report eGFR as part of the routine blood chemistry results, so identifying patients at risk should not be difficult.

Does this apply to transplant patients?

Drug dose adjustment also applies to transplant patients. The majority of transplant patients do not have a normal eGFR. Renal function often stabilizes at stage 2 to 4, depending on the patient. Drug dosing should follow the same rules as in CKD patients, with special consideration to agents that can alter the metabolism of the immunosuppressant agents.

Do transplant patients have special considerations?

Transplant patients are often taking calcineurin inhibitors. Given that these immunosuppressant agents use the hepatic cytochrome pathways for their metabolism, medications that compete for these pathways may result either in toxicity from a decrease in their rate of metabolism or in low levels of these immunosuppressant agents and a resultant increased risk of rejection caused by an increased rate of their clearance.

What types of symptoms can inappropriate dosing cause in these patients?

Manifestations can include altered mental status, abnormal motor activity, seizures, acute renal failure, acute hepatitis, dermatitis, mucositis, and bone marrow suppression.

Is any class of drugs particularly harmful?

Some examples of class effect include antivirals, anticonvulsants, macrolide antibiotics, nonsteroidal agents, Cox-2 inhibitors, and metformin.

Should any drugs in particular not be used?

Owing to their effects on GFR, Cox-2 inhibitors and nonsteroidal agents should be avoided. Metformin should be avoided if the creatinine determination does not meet the criteria for metformin use. Other drugs can be used if appropriately dose modified or, in the case of transplant recipients, if the immunosuppressant medication levels are measured appropriately.

How can you treat an unintended reaction caused by dosing issues in CKD, ESRD, and transplant patients?

Treatment involves a variety of strategies depending on the situation and can include stopping the medication, giving supportive care, adjusting immunosuppressant medications, or administering dialysis to remove the offending agent.

When does a patient with ESRD need to take certain drugs in relation to hemodialysis or peritoneal dialysis?

Drugs that have significant renal clearance should be taken after hemodialysis. For peritoneal dialysis, when possible, drugs that are renally cleared should be taken after the completion of continuous cycling peritoneal dialysis. Dosing should be for GFR <10 mL/min/1.73 m^2.

Does this apply to hospitalized patients receiving continuous renal-replacement therapy?

Dosing considerations also apply to these patients. Consultation with the hospital pharmacy should occur to ensure that the proper prescription is given to the patient receiving continuous renal replacement therapy.

Where can providers get information on dosing guidelines?

With the advent of the Internet and the multitude of hand-held devices available, information is almost always readily accessible. Useful sites, to name a few, include UpToDate, mobile PDR (Physician's Desk Reference), MPR (Monthly Prescribing Reference), Epocrates, and Medscape.

What would be your general recommendations to make things easier for providers?

Note that eGFR is the first step in making life easier for providers. Providers should do a quick lookup in one of the many available online references when prescribing medications with which they are unfamiliar. Providers should find a reference that they believe is quick and easy to use and have it available on their computer desktops or as an app on their hand-held devices. For children younger than 17, the Schwartz formula should be used to estimate eGFR. It is available online.

Recommended sources

http://www.UpToDate.com
http://www.Medscape.com
http://www.PDR.net
http://www.Epocrates.com
http://www.eMPR.com

Eugene C. Kovalik, MD, is associate professor of medicine at Duke University Medical Center.

NephroTalk: Train the Trainers' Communication Workshop for Nephrology Educators Slated for Spring 2015

The ability to effectively communicate with patients and their families is an essential skill for nephrologists. Available data suggest that effective communication can strengthen patient and family participation in treatment decisions and enhance a patient's experiences and care at the end of life. Effective communication is often viewed as an inherent skill that a person either possesses or lacks. However, a growing body of work suggests that these skills can be taught. Within nephrology education, Dr. Jane Schell and colleagues developed NephroTalk, a communication workshop designed to teach effective communication skills to nephrology fellows.

Effective communication skills are especially critical in discussions about end-of-life preferences and advance care planning (ACP). Data suggest that most patients with ESRD have not engaged in ACP and are unprepared for the kinds of treatment decisions that they may face toward the end of life. In a recent study of care received by older Medicare beneficiaries during the final month of life, patients with ESRD were more likely to receive intensive interventions such as intubation and cardiopulmonary resuscitation and less likely to receive hospice services compared with other patients with life-limiting conditions. These intensive patterns of end-of-life care may highlight an important opportunity to enhance ACP in this population to ensure that patients are receiving care that is congruent with their preferences. Available data in this population, as in other populations, suggest that timely conversations about the end of life and ACP have been associated with high-quality end-of-life care and improved caregiver outcomes. Collectively, these realities signal the need for efforts to enhance ACP in this population.

In spring 2015, the American Society of Nephrology (ASN) will sponsor a workshop entitled "NephroTalk: Train the Trainers' Communication Workshop for Nephrology Educators." This 3-day workshop will adapt the original NephroTalk workshop to teach attendees the communication skills necessary to both engage in ACP with their own patients and teach these communication skills to trainees. The Train the Trainers workshop is targeted at nephrology educators who wish to teach communication skills at their own institutions (e.g., faculty-level physicians and advance practitioners). Teaching faculty will include members of VitalTalk, the nonprofit communication entity that developed NephroTalk. The content focus of the workshop will be hands-on learning of communication skills with specific relevance to ACP in older adults with advanced kidney disease.

The workshop will be held April 27 to 29, 2015, in Pittsburgh, PA. ASN will cover the cost of the workshop for up to 10 participants and will provide each participant with a stipend of at least $800 to defray the costs of travel. Preference will be given to applicants who demonstrate an interest in promoting and developing communication education at their home institutions and who can demonstrate the institutional support needed to accomplish this goal. A request for applications will be posted on the ASN website at the end of July 2014. For more information about the workshop and application requirements, please email ASN Policy Associate Mark Lukaszewski at mlukaszewski@asn-online.org.

Journal View

Off-Pump CABG Reduces AKI Risk—But No Difference in Later Kidney Function

Patients assigned to off-pump coronary artery bypass grafting (CABG) have a lower risk of acute kidney injury (AKI) but no reduction in the rate of reduced kidney function 1 year later, reports a study in the *Journal of the American Medical Association.*

In the international randomized trial, 4752 patients undergoing their first isolated CABG procedure were assigned to the off-pump (beating-heart) technique or to on-pump cardiopulmonary bypass. A kidney function substudy analyzed serum creatinine data during the postoperative period and at 1-year follow-up in 2932 patients. The two groups were compared for their risk of AKI at 30 days, defined as a 50 percent or greater increase in serum creatinine level. The 1-year rate of loss of kidney function—a 20 percent or greater reduction in estimated GFR—was also compared between groups.

The 30-day AKI risk was 17.5 percent in patients assigned to off-pump CABG versus 20.8 percent in the on-pump group: adjusted relative risk (RR) 0.83. However, the reduction in AKI did not lead to a reduced risk of kidney function loss at 1 year: 17.1 and 15.3 percent, respectively.

A subgroup analysis of patients who had chronic kidney disease at baseline showed an even greater reduction in AKI risk with off-pump CABG: 19.2 versus 30.2 percent, RR 0.63. In both analyses, the results were similar when different definitions of AKI were used.

Cardiac surgery is associated with a substantial risk of mild to moderate AKI, but the implications for long-term kidney function are unclear. No intervention that lowers the risk of AKI has been proved to protect long-term kidney function.

The new trial shows a lower 30-day risk of AKI in patients undergoing off-pump CABG rather than the on-pump procedure. However, this does not lead to any difference in the rate of reduced kidney function at 1-year follow-up. The researchers write, "[T]he findings emphasize proof is needed to claim an intervention that reduces the risk of mild acute kidney injury better preserves long-term kidney function for the group that received it" [Garg AX, et al. Kidney function after off-pump or on-pump coronary artery bypass graft surgery: a randomized clinical trial. *JAMA* 2014; 311:2191–2198].

Rising Diabetes Rates in American Children and Teens

The prevalence of both type 1 and type 2 diabetes among American youth increased significantly during the past decade, according to a report in the *Journal of the American Medical Association*.

The SEARCH for Diabetes in Youth study analyzed data on diabetes prevalence from 2001 to 2009 among children and adolescents in four geographic areas of the United States, including American Indian reservations in two states, and from a large California healthcare system. Trends in the prevalence of physician-diagnosed type 1 diabetes from age 0 to 19 years and type 2 diabetes from age 10 through 19 years were analyzed.

The prevalence of type 1 diabetes (per 1000) increased from 1.48 in 2001 to 1.93 in 2009. Type 1 diabetes was most frequent in white children and adolescents and least frequent in American Indian youth: 2.55 versus 0.35 per 1000, respectively. Prevalence increased in nearly all age, sex, and racial and ethnic groups. On adjusted analysis, the increase in type 1 diabetes prevalence was 21.9 percent.

The prevalence of type 2 diabetes also increased: from 0.34 to 0.46 per 1000. By racial and ethnic groups, the rates per 1000 were 1.20 for American Indian, 1.06 for black, 0.79 for Hispanic, and 0.17 for white youth. The adjusted increase in the prevalence of type 2 diabetes was 30.5 percent.

The study supplies needed data on trends in diabetes rates among children and adolescents in the United States. The results suggest that the prevalence of type 1 diabetes increased by about 20 percent and of type 2 diabetes by 30 percent during the previous decade, with significant variations by race and ethnicity. Further study will be needed to determine the cause of the rising diabetes rates in young Americans [Dabelea D, et al. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. *JAMA* 2014; 311:1778–1786].

Autopsy Study Looks at Kidney Damage in Drug Abusers

Illicit drug abuse is associated with a "broad but unspecific" range of pathologic changes in the kidneys, according to a postmortem analysis in the *American Journal of Kidney Diseases*.

The researchers analyzed the renal findings at forensic autopsy in 129 individuals who died of causes related to illicit drug abuse in one German city between 2009 and 2011. The mean age was 39 years, and 82 percent of the decedents were male. Eighty percent were intravenous drug users. The average known duration of drug use was 17 years. Toxicologic analyses showed a broad spectrum of substances, most commonly opioids, cocaine, and alcohol.

Comorbid conditions included cardiovascular disease, cirrhosis, and infections. Pathologic findings in the kidneys included arteriosclerotic and ischemic damage, mild interstitial inflammation, parenchymal calcification, and interstitial fibrosis and tubular atrophy. The most common cause of nephropathy was hypertensive-ischemic.

Pathologic findings associated with severe intravenous drug use included interstitial fibrosis, odds ratio (OR) 16.59; and renal calcification, OR 2.43. By contrast, cocaine abuse was associated with hypertensive and ischemic damage, OR 6.00. There was no evidence of specific glomerular damage associated with heroin-related or hepatitis C virus–related disease, or of analgesic nephropathy.

Abuse of illicit drugs is a known risk factor for chronic kidney disease, but few studies have examined the renal consequences of long-term drug abuse. This autopsy study shows a broad but nonspecific range of nephropathy in a group of young individuals who died of causes related to drug abuse.

Drug abusers may sustain chronic progressive kidney damage related to "multiple pharmacologic challenges" over time, the researchers write. Cocaine abuse may promote kidney disease progression by inducing hypertensive and ischemic damage [Buettner M, et al. Nephropathy in illicit drug abusers: a postmortem analysis. *Am J Kidney Dis* 2014; 63:945–953].

High Rate of Cancer-Related Death after Kidney Transplant

Kidney transplant recipients are at high risk of malignancy-related death, and this risk may be higher in recipients of organs from deceased donors, reports a study in *Kidney International*.

The researchers analyzed data on all kidney-only transplantations performed in England from 2001 to 2012, with linkage to hospital and mortality data. The study included 19,103 kidney transplant procedures, and the median follow-up time was 4.4 years. The analysis focused on the overall and site-specific risks of malignancy-related death, along with associated factors.

Of 2085 deaths during follow-up, 18 percent were malignancy-related, for a crude mortality rate of 361 deaths for 100,000 person-years. Lymphoma and lung cancer were the most common malignancies: 18.4 and 17.6 percent, respectively; followed by renal cancer, 9.8 percent; and unspecified cancers, 14.1 percent. Malignancy-related mortality was 0.8 percent for recipients younger than 50 years, 2.5 percent at ages 50 to 59, 4.8 percent at ages 60 to 69, 6.5 percent at ages 70 to 79, and 9.1 percent at age 80 or older.

When patients were stratified for age and sex, the risk of malignancy-related death was significantly higher in transplant recipients than in the general population. Independent risk factors included older age, history of cancer before transplantation, and receipt of organs from deceased donors.

Kidney transplant recipients are at increased risk of cancer, reflecting the effects of immunosuppression. Few data are available on the risk of malignancy-related mortality after transplantation.

The new results show that malignancy is a common cause of death after kidney transplantation. Although the increased risks associated with age and previous cancer history are expected, the link to deceased-donor organ transplantation is not. The findings underscore the importance of targeted surveillance after transplantation [Farrugia D, et al. Malignancy-related mortality following kidney transplantation is common. *Kidney Int* 2014; 85:1395–1403].

Industry Spotlight

Dialysis Drug Recall in Tennessee

A Fresenius product used in dialysis was recalled after one death by bacterial infection and other cases of sickness after certain lots of the drug were administered.

The U.S. Food and Drug Administration (FDA) issued the class 1 recall related to the use of Fresenius NaturaLyte Liquid Bicarbonate Concentrate. The FDA reported that laboratory tests identified *Halmonas* species, a bacterial strain typically found in water with a high salt concentration, in the product during its shelf life.

Fresenius noted in its recall announcement that according to the medical literature, bacterial contamination of the dialysate may lead to bacteremia or systemic infection, although "the dialysis filter (dialyzer) and the use of the Diasafe filter or equivalent create an effective bacteria and endotoxin barrier that makes this event unlikely."

The *Tennessean* newspaper wrote that 26 dialysis centers in Tennessee were among those receiving the product.

"We have notified all of our affected customers that the recalled product should be removed and are continuing to work with them to carry out the recall," a Fresenius representative said. The affected lots were produced in the Fresenius facility in Montreal, Canada.

First Hemodiafiltration in the United States

DaVita started using the Nephros hemodiafiltration system in a pilot program based in its Colorado Springs facility to learn how the system compares with traditional hemodialysis in patient care. Nephros gained approval from the FDA in 2012 for the hemodiafiltration system, which may enhance traditional hemodialysis by filtering out a range of different-sized contaminants.

This program is the first commercial use of hemodiafiltration in the United States. The method has been approved and used in European dialysis settings for several years. Whereas dialysis works on a diffusion principle (carrying small waste molecules through a filter as a result of a solvent gradient that depends on differences in concentration to remove waste from blood), hemodiafiltration provides an extra boost of cleansing because of convection—moving molecules through a fluid under pressure and forcing out the large waste molecules, which are too large to be removed through the traditional diffusion principle.

The Nephros OLpūr MD Mid-Dilution HDF Filter is used to gain urea clearance of postdilution hemodiafiltration. The system maintains a proper fluid balance for the patient while offering clearance of toxins in the middle-molecule range. For a schematic of the system, visit http://www.nephros.com/dialysis/hemodiafiltration/hdf-explained/

According to a 2006 study published in *Nature*, patients receiving high-efficiency hemodiafiltration had a significantly lower risk of mortality (35 percent) than did those receiving low-flux hemodialysis ($p = 0.01$). The observational results suggested that some aspect of hemodiafiltration may improve patient survival independently of its higher dose of waste removal.

To date, the Nephros system is the only one approved in the United States; Fresenius has a hemodiafiltration system in use in Europe that has not yet been approved by the FDA.

CJASN and JASN
for iOS and Android

The CJASN and JASN mobile applications allow readers to access the latest nephrology research and commentary published in the Clinical Journal of the American Society of Nephrology and the Journal of the American Society of Nephrology from anywhere in the world.

Kidney News for iOS and Android

Kidney News is your source for information in the world of nephrology. This app features the latest issues of Kidney News and allows you to search articles and bookmark favorites.

To download these and other ASN media, visit www.asn-online.org/media.

Available on the iPhone App Store

ANDROID APP ON Google play

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Classified Ads

Kidney News
Classified Advertising Information

Classified space is for advertising positions available, open faculty positions, course announcements, seminars, meetings and educational courses.

Display Advertising Rates

Ad Size	1x	3x
Full Page	**$2,525**	**$2,345**
1/2 Page	$1,665	$1,485
1/3 Page	**$1,435**	**$1,375**
1/4 Page	$1,205	$1,090
1/6 Page	**$1,035**	**$1,025**

Line Advertising Rates

Please contact for rate information

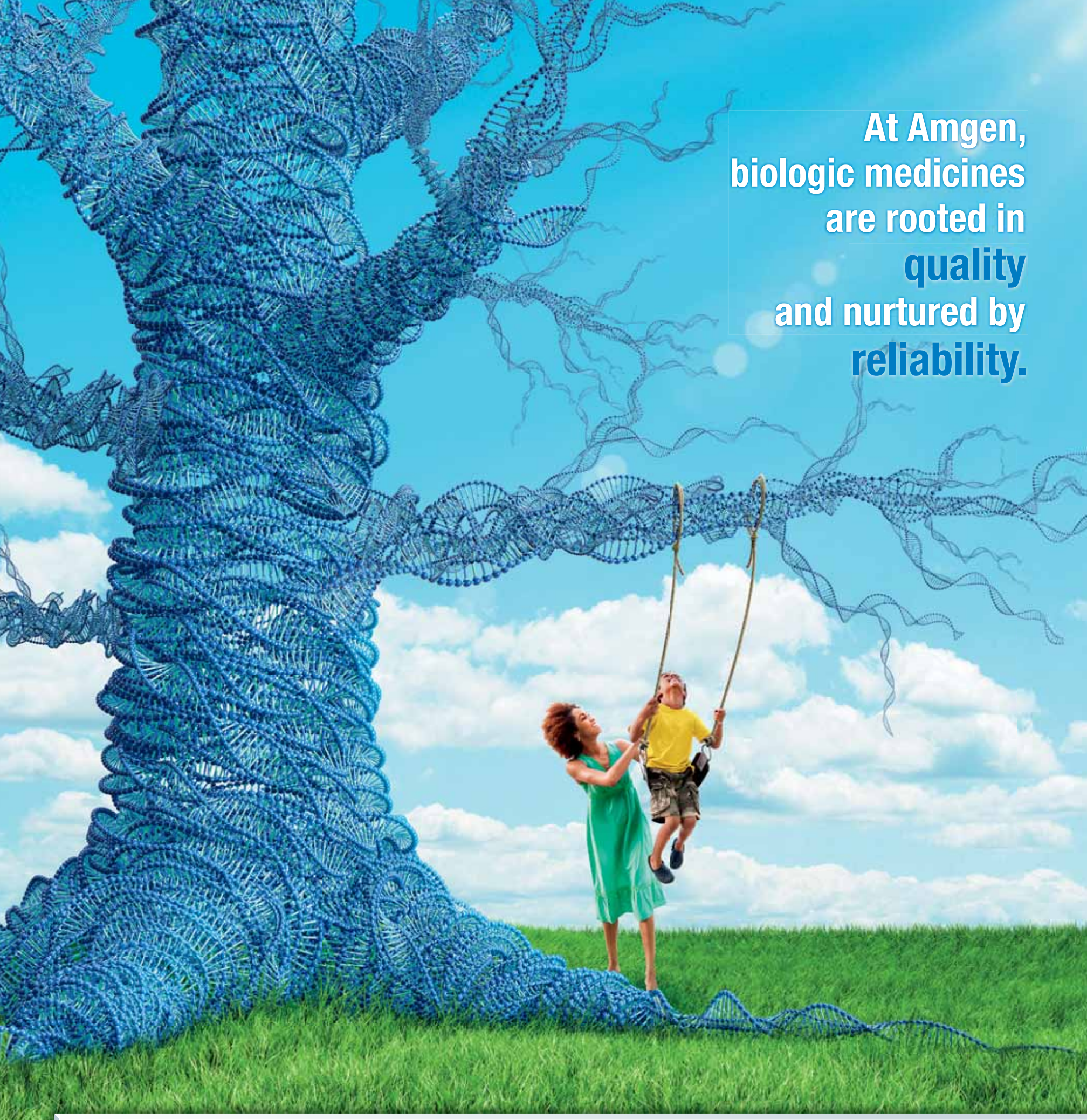
Closing Date & Cancellations:

Copy must be received four weeks in advance of the month in which the ad is to appear. Cancellation requests must be made in written form by fax, e-mail or postal mail and will be honored for the earliest applicable issue.

All Ads Must be Prepaid

Contact:
Rhonda Truitt
rhonda.truitt@wt-group.com
P: 443-512-8899 x. 106 F: 443-512-8909

Index to Advertisers



Robust quality control and a reliable supply are every bit as important as scientific innovation.

For more than 30 years, Amgen has poured commitment, passion, and a drive for perfection into every medicine we make.

So you can turn to Amgen for the biologic medicines that matter so much to your patients' treatment…for generations to come.

To learn more about Amgen's commitment to consistent quality and reliable supply, visit biotechnologybyamgen.com

BIOTECHNOLOGY BY AMGEN®