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ADVANCES IN NEPHROLOGY

Affiliated with Columbia University College of Physicians and Surgeons and Weill Cornell Medical College

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An Influential Bench-to-Bedside Resource in Glomerular Diseases

When NewYork-Presbyterian/Columbia University Medical Center established the Center for Glomerular Diseases some 15 years ago, it was the first of its kind in the country to foster research and treatment of these diseases. A collaboration of the Divisions of Nephrology and Renal Pathology at NewYork-Presbyterian/Columbia, today the Center cares for some 3,000 patients annually. With Renal Pathology, the Center performs, processes, and studies over 4,000 biopsies a year.

"Patients come to the Center from all over the country and the world," says **Gerald B. Appel, MD**, Director of Clinical Nephrology at NewYork-Presbyterian/Columbia, and Co-Director of the Center for Glomerular Diseases, along with **Ali G. Gharavi, MD,** Chief of Nephrology at NewYork-Presbyterian/Columbia. "Here we bring the highest quality science to bear on the clinical perspective of glomerular diseases to ensure an accurate diagnosis and by extension the right treatment."

A major strength of the Center for Glomerular Diseases lies in the five full-time nephrologists devoted to caring for these patients, from initial consultation and biopsy,

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Dr. Andrew S. Bomback and Dr. Gerald B. Appel

Emerging Strategies to Transplant the Untransplantable

Approximately 30 percent of patients needing a kidney transplant are unable to receive a kidney from a willing family member or a friend because of blood group (ABO) incompatibility with their potential kidney donor or because they have anti-HLA antibodies directed against their donors. "For these patients, we have developed strategies to overcome the existing barriers; our approach includes identifying those at high risk of developing rejection following transplantation and initiating preemptive therapy," says **Darshana M. Dadhania, MD**, a specialist in transplant nephrology with NewYork-Presbyterian/Weill Cornell Medical Center. In general, living donor kidneys are associated with a much better survival compared with deceased donor kidneys. "However, patients who have donor-specific antibodies are at even higher risk of acute rejection and, as a result, graft failure."

> "Our strategy offers a new, simple, and testable approach to manage sensitized patients and may stimulate studies to investigate effectiveness of new treatment protocols in patients identified to be at high risk for antibody-mediated rejection and graft failure."
> — Dr. Darshana M. Dadhania

According to Dr. Dadhania, recipients who enter into a transplant with high levels of donor-specific antibodies can develop additional antibodies if their kidney transplant fails. "This will make it even more difficult for that recipient to obtain another transplant," notes Dr. Dadhania.

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NewYork-Presbyterian Nephrology ranks #3 in the nation.

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An Influential Bench-to-Bedside Resource in Glomerular Diseases *(continued from page 1)*

to establishing a diagnosis and formulating a treatment plan, to following them through the entire disease course. In addition, Columbia's renal pathology group – with six renal pathologists – is considered one of the best in the world. "A combination of clinicians, pathologists, and researchers dedicated to these diseases enables us to take care of patients in a way that can't be done elsewhere," says Dr. Appel.

"These are generally rare disorders of kidney inflammation that are not seen on a regular basis in the community," adds **Andrew S. Bomback, MD, MPH**, a nephrologist who specializes in glomerular diseases and resistant hypertension. "While a community nephrologist may only see one or two cases a month, on a daily basis we see 10 to 15. When you care for such a large volume of patients, even with such rare diseases, in addition to building up a strong clinical experience, it allows you to do the best possible research studies, to get patients into clinical trials, to do your own epidemiological studies, and establish registries for studying relationships between renal histopathology and clinical features, disease course, and patient outcomes."

From Broad-Based Research to Advancing Therapeutics

As the Center for Glomerular Diseases has expanded over the years, so has research funding. "At any one time, we are running 15 to 20 studies sponsored by the National Institutes of Health, pharmaceutical companies, and independent investigations on different diseases of the glomerular filters," says Dr. Appel. "We are continually studying immunomodulatory drugs and are often at the forefront of using newer immunosuppressive medications that hopefully will have fewer side effects and be more effective."

Additionally, collaboration with basic scientists is underway to explore noninvasive routes to diagnose a glomerular disease via a blood or a urine test and offer a more personalized approach for each patient. The Glomerular Center's physicians, in collaboration with the Gharavi laboratory, are pioneering the application of the latest genomic technologies for diagnosis of glomerular disorders. By using whole genome sequencing, investigators are able to precisely diagnose diseases and, in some cases, precisely tailor treatment to the underlying molecular lesion. These efforts are expected to set the standards for the care of patients with glomerulopathies and transform the daily practice of nephrology.

"For IgA and membranous nephropathies, I think we are on the cusp of being able to offer these less invasive diagnostic methods," says Dr. Bomback. "For other diseases, such as minimal change disease and focal segmental glomerulosclerosis, while we have a way to go before entering the clinical setting, we are pursuing research protocols that will help define biomarkers for these diseases."

In the translational and clinical arenas, investigations are focused on the major glomerular diseases, including focal glomerulosclerosis, diabetic nephropathy, membranous nephropathy, IgA nephropathy, and many patterns of lupus nephritis.

"The Center for Glomerular Diseases has actually led the charge in many of the landmark clinical trials over the last decade in lupus," notes Dr. Bomback. "These include, for example, studies that have established mycophenolate mofetil as a first-line therapy in place of chemotherapy for lupus nephritis. We are still seeing many referrals for patients with lupus nephritis who have failed first- and second-line therapy. In these cases, we may combine currently available immunosuppressive agents or enroll them in clinical trials where they have access to the newest biologic agents.

"For any patient who is referred to the Center, one of our initial branch points is 'Does this patient need to be treated with immunosuppressive therapy?' It is a major decision on whether or not to put patients on strong medicine with a number of potential toxicities," says Dr. Bomback. "Once we have made that decision then there are a number of immunosuppressive therapies that we have to choose from. This is what I'd call the 'artistry' of what we are able do here at the Glomerular Center: Take these very powerful therapies and tailor them to individual patient circumstances."

Under the leadership of Dr. Gharavi, who serves as a principal investigator, the Hospital is a clinical site for a multicenter five-year cohort study of patients with glomerular disease funded by the National Institute of Diabetes and Digestive and Kidney Diseases. This major initiative, the Cure Glomerulonephropathy (CureGN) Study, seeks to uncover the causes of glomerular diseases and understand response to therapy and disease progression. The study, which began in December 2014, will follow 2,400 children and adults across the country, including 600 patients at Columbia, with minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, and IgA nephropathy. It is the largest cohort to date of glomerular diseases.

"This is a huge endeavor," says Dr. Bomback, co-investigator of the study. "With such a large number of patients, we will be building an enormous biorepository upon which further studies can be done in addition to defining the natural history of these four diseases. We like to have at least one trial for each disease so that whenever patients are referred to us for second or third opinions and they are running out of treatment options, we can always offer them the opportunity to participate in a clinical trial of a novel therapy. In many cases, patients are looking to see if there are other options available and that is why they come to us."

"It's a very exciting time for nephrology," adds Dr. Appel. "The bottom line is helping our patients. Everything we do here is directed at drawing on science to provide excellent care for patients with kidney disease."

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Emerging Strategies to Transplant the Untransplantable *(continued from page 1)*

"So our current strategy is to identify the best transplant option for the patient and minimize the patient's risk of acute rejection and graft loss."

In a recently completed study published in *Transplantation*, Dr. Dadhania and her colleagues sought to clarify characteristics of pre-transplant antibodies directed at donor human leukocyte antigen (HLA) donor-specific antibodies (DSA) that are associated with adverse outcomes in kidney transplant recipients. The researchers prospectively screened pre-transplant sera from 543 kidney recipients who underwent transplantation at NewYork-Presbyterian/Weill Cornell. Using single antigen bead assays, they identified 154 patients with DSA and 389 without DSA. They then investigated the association of DSA features to acute rejection and graft failure.

Dr. Darshana M. Dadhania

"We found that the one-year acute rejection incidence was higher in the DSA-positive group, primarily due to antibody-mediated rejection and not T cell-mediated rejection," notes Dr. Dadhania. Their strategy identified that the sum of mean fluorescence intensity (MFI) of DSA of 3,000 or higher, but not less than 3,000, is associated with an increased risk of antibody-mediated rejection (AMR), and further revealed that the DSA MFI-Sum of 6,000 or higher and the presence of DSA against both HLA class I and II predicted one-year AMR independent of other variables.

"We also found that the association with graft loss is not independent of an episode of AMR within the first year," adds Dr. Dadhania. "This suggests that the mechanism by which DSA confers an increased risk of graft loss is through its effect on AMR risk. Additionally, our observations have the potential to be clinically directive. Specifically, patients with pre-transplant DSA MFI-Sum less than 3,000 or DSA against HLA class I alone or II alone are not at increased risk for AMR and therefore do not require preemptive therapy."

Dr. Dadhania and her colleagues believe that this study offers a new algorithm for classifying DSA positive patients as those at risk for AMR and graft failure and those not at risk. "An important goal of screening patients for DSA is to identify patients at risk for acute rejection and initiate preemptive or adjunctive therapy to reduce the risk," says Dr. Dadhania. "Our strategy offers a new, simple, and testable approach to manage sensitized patients and may stimulate studies to investigate the effectiveness of new treatment plans, for example, bortezomib, in patients identified to be at high risk for AMR and graft failure."

Match Makers

With their first priority to facilitate transplantation with the best outcomes for sensitized patients, an important aspect of the strategy of Weill Cornell's transplant nephrologists is improving the donor match. This is being accomplished through their burgeoning Kidney Paired Donation Program, a program in which kidneys are swapped among donor-recipient pairs. Patients with DSA and/or a positive flow cytometry cross match against their potential living donor are encouraged to enter the Kidney Paired Donation Program. "As part of this program, we identify potential donors who are completely compatible with the recipient – ABO-compatible and cross-match compatible. If that is not possible, which is the case for about 20 percent of patients, then we move to identifying a 'more' compatible donor, one associated with significantly lower risk of acute rejection and graft loss, compared to their patient's own living donor."

During the first three months that patients are in the Kidney Paired Donation Program, the transplant team uses the most stringent criteria to identify the best donor, one associated with low immunologic risk. "If we are not able to identify a completely 'clean' donor, we extend the protocol to include preconditioning therapy for the patient while we locate a donor that is more suitable," says Dr. Dadhania. "Since 2006, we have been using a combination of rituximab and IVIG as a preconditioning therapy. Our data suggest that this approach lowers the incidence of acute rejection. Since 2008, we have enrolled over 125 incompatible individuals into the program, and we have transplanted more than 90 percent of them within a year of entry."

What makes the program at NewYork-Presbyterian unique is a multidisciplinary team of experts who are actively involved in the care of sensitized patients. They have been trained not only as transplant physicians and immunologists, but also as experts in histocompatibility. "There are only a handful of physicians or transplant nephrologists who have this training, and two are here at our center," notes Dr. Dadhania.

Weill Cornell's team is led by **Sandip Kapur, MD**, Chief of Transplant Surgery and Director of the Kidney and Pancreas Transplant Programs; **Manikkam Suthanthiran, MD**, Chief of Transplantation Medicine, Nephrology and Hypertension; **Darshana Dadhania, MD**, Medical Director, Histoincompatible Kidney Transplant Program; and **Vijay K. Sharma, PhD**, Director of the Rogosin Institute Immunogenetics and Transplantation Laboratory. The program performs over 200 transplants a year and has an active post-transplant monitoring protocol for sensitized patients that facilitates early detection of immunological events and delivery of personalized care. "Having one immunological event, such as an acute rejection episode, can decrease the life of that kidney," says Dr. Dadhania. "Close monitoring is the key to long-term success."

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C3 Glomerulopathy: Cracking the Genetic Code

C3 glomerulopathy – a very rare form of kidney disease exemplified by dense deposit disease and C3 glomerulonephritis – is a recent disease classification first described in the medical literature in 2007. Its incidence is estimated at one to two cases per million.

"We are still gathering data on C3 glomerulopathies in order to correlate findings on genetic, autoantibody, and complement function screening with the prognosis or progression of disease," says **Dr. Gerald Appel**, who was an invited expert to the first C3 Glomerulopathy Meeting panel, which met in 2012 to develop a consensus on the definition, studies, and therapeutics related to the newly defined disease. "As the number of identified cases increases, it is likely that some of these pathogenetic parameters will be found to be biomarkers of disease progression. In small series of patients, however, the best available predictors remain the standard clinical parameters, such as degree of renal dysfunction, measured by serum creatinine or estimated glomerular filtration rate, and proteinuria at the time of diagnosis."

"In the last two years, we have seen over 100 patients with this disease," says **Dr. Andrew Bomback**. "They are being referred because their doctors don't know what to make of this new diagnosis. We believe many of these cases are due to a genetic predisposition or mutation, and so in collaboration with our genetics and precision medicine initiatives in the Department of Medicine and Division of Nephrology, we are doing whole genome sequencing on all patients we see with C3 glomerulopathy. We expect that we will be able to 'crack' the genetic code to determine the exact location of the defect in their alternative complement pathway, which is presumed to be hyperactive in these patients. A very important component of the management of these and other patients with glomerular disease going forward will be to offer whole genome sequencing when any unexplained form of kidney failure is present."

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