Advances in Autosomal Dominant Polycystic Kidney Disease

William E. Braun, M.D.

Autosomal Dominant Polycystic Kidney Disease (ADPKD) affects approximately 600,000 to 700,000 people in the United States, with about 5,000 to 6,000 new cases seen each year. Forty percent of patients are diagnosed by the age of 45, and 60% have a positive family history of ADPKD. Between 5% and 10% of renal transplant recipients have had ADPKD as the cause of their kidney failure.

The clinical picture of ADPKD has two major aspects: cysts and their complications, and non-cystic features. The cysts in ADPKD involve both kidneys, usually the liver, and other sites much less frequently. In addition to progressive kidney enlargement and eventual deterioration of renal function, polycystic kidney complications include a higher frequency of renal stones (uric acid and calcium oxalate), urinary tract infections (UTI), episodes of bleeding that may or may not be associated with gross hematuria, and varying degrees of abdominal and flank pain associated with progressive enlargement of the kidneys.

Non-cystic features of ADPKD include the occurrence of intracranial aneurysms (with a higher frequency if there is a history of an intracranial aneurysm in conjunction with ADPKD in another family member), cardiac valve abnormalities in about one-third of patients (usually mitral valve prolapse, which is often mild but still requires the use of prophylactic antibiotics), and hernias.

The two main genetic types of ADPKD are PKD1 and PKD 2. PKD1 occurs because of a mutation on the 16th chromosome, is responsible for about 85% of all ADPKD cases, and progresses to end-stage renal disease (ESRD) usually when patients are in their early 50s. PKD2 is caused by a mutation on the 4th chromosome, affects about 15% of patients with ADPKD, and tends to cause ESRD more slowly, often around age 70. The distinction between the time course of PKD1 and PKD2 progression to ESRD can be blurred by the occurrence of what have been called “second hits.” In addition to the inherited germline mutation on chromosome 16 or 4 that constitutes the primary genetic abnormality in ADPKD, the “normal” chromosome 16 or 4 from the healthy parent is susceptible to later somatic mutations that ultimately lead to the development of individual renal cysts. Because the nature of these second hits is unknown and unpredictable, the time course of PKD1 and PKD2 ADPKD may vary considerably even within the same family.

Recent studies of ADPKD patients have confirmed that: patients with PKD1 tend to form cysts at an earlier age and in greater number than do patients with PKD2; the volume of polycystic kidneys is a major determinant of the rate
Table of Contents

New Approaches to Assessing the Hypertensive Patient 5
Identifying Risk for Rejection of Transplanted Kidneys 6
News Affecting the Practice of Nephrology 8
An Implantable Membrane Could Shift Treatment of Kidney Failure 9
High-Renal-Risk Patients: Pre-Procedure “Clearance” and Follow-Up 10
Novel Treatment for Diabetic Nephropathy 12
Fellows Corner: An Update on the Program in Nephrology and Hypertension 13
Clinical Trials 14
Publications 15
New Staff 16
Staff Directory 18

The Glickman Tower, scheduled to be completed in 2008, will be the new home of the Glickman Urological and Kidney Institute, which includes the Department of Nephrology and Hypertension and the departments of Urology and Regional Urology.
Dear Colleagues,

Beginning in the fall of 2005, we began reshaping the Department of Nephrology and Hypertension at Cleveland Clinic to achieve a signature experience for faculty, fellows and patients that would set us apart from other major healthcare institutions. I believed that it was critical to recruit talented scientists and clinical faculty essential for addressing impact scientific questions, examine newer patient care models that focused on achieving superior outcomes, and develop key affiliations within the Lerner Research Institute that would foster translational scientific discovery and provide research opportunities for our fellows.

A number of gifted scientists and clinicians have been recruited over the past year: Qingyu Wu, M.D., Ph.D., Sevag Demirjian, M.D., Priya Kalahasti, M.D., and Chris Hebert, M.D., joined the department in 2006 while Bill Fissell, M.D., Jim Simon, M.D., Mohammed Rafey, M.D., and Martin Lascano, M.D., have arrived during 2007. We are excited about these additions and look forward to additional recruits in transplantation, regenerative medicine and regional nephrology during the next year.

Research activities within the department are now focused in the areas of polycystic kidney disease, bioartificial extracorporeal systems, hypertension/nephrosclerosis, chronic kidney disease, acute kidney injury and transplantation immunology. Department faculty are active contributors to the curriculum of the Cleveland Clinic Lerner College of Medicine and remain committed to both the residency and the nephrology fellowship training programs. We continue to attract exceptional fellowship candidates and have redesigned the nephrology training program with the goal of training the very best nephrologists.

We will need innovative models of health management in the future. These newer models will require that we view patients differently, develop health management teams that teach patients a greater understanding of their disease and involve patients more than ever in their ongoing treatment. While physicians play a key role in designing treatment plans, the additional task of educating patients and their families and ensuring the treatment plan is carried out will require the further talent of nurse practitioners, physician assistants, nutritionists and educators each with a specific role on the health management team.

Cleveland Clinic’s Board of Governors has reorganized Cleveland Clinic’s structure into institutes committed to differentiating patient care into the future. This new disease-organ-based institute structure will replace the traditional Divisions of Medicine and Surgery at Cleveland Clinic. The new Glickman Urological and Kidney Institute will include the departments of Nephrology and Hypertension, Urology and Regional Urology. The institute will move into the newly constructed Glickman Tower in the fall of 2008.

The Department of Nephrology and Hypertension will begin providing clinical expertise in Cleveland Clinic’s regional family health centers and provide care options in the Cleveland Clinic system hospitals. Basic science and clinical research will be focused at the main campus along with consultative services and established follow-up care. The expansion will define a new approach to linking the community with the main campus and improve access and research opportunities for a broader group of patients.

Thank you for your continued professional encouragement, clinical referrals and research financial support.

Sincerely yours,

Martin Schreiber, Jr., M.D.,
Chairman, Department of Nephrology and Hypertension
Glickman Urological and Kidney Institute
of decline in kidney function; and combined kidney sizes exceeding 1,500 ml are associated with accelerated loss of kidney function and decreases in glomerular filtration rate of approximately 5 ml/year.

Treatment of the renal component of ADPKD has two major areas: standard therapy and trials of newer therapies. Standard therapy includes treatment of hypertension, kidney stones, UTI, pain and ESRD with dialysis and/or transplantation. Early rigorous control of hypertension may slow the loss of renal function. The preferred antihypertensive medications are angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB). Fluid and diet modifications may be useful. A low-sodium diet is important for control of hypertension and may also slow the expansion of renal cysts. Caffeine should be avoided in the diet because it interferes with the downregulation of cyclic AMP that is a major factor in cyst formation. If the patient’s renal, cardiac and pulmonary status permit, a high fluid intake of 2,500 to 3,000 cc of water should be taken daily. High fluid intake helps to suppress vasopressin, one of several mediators that can stimulate cyclic AMP and lead to cyst formation.

Encouraging results in experimental animal models of ADPKD have stimulated trials of new treatments in patients with ADPKD. Because ACE inhibitors, and possibly ARB, have not only antihypertensive effects but also the ability to slow cyst enlargement and preserve renal function in PKD animal models, these medications (lisinopril plus telmisartan or placebo) are now being studied in an NIH-sponsored nationwide trial in which Cleveland Clinic is participating. In a second study under way as a pilot study at Cleveland Clinic, the immunosuppressive medication rapamycin (sirolimus, Rapamune®) is being studied because in animal models of PKD it decreased renal cyst and kidney sizes. Rapamycin has unique properties of inhibiting cell proliferation (antiproliferative) and excessive small blood vessel development (antiangiogenic), two factors that promote ADPKD. In the Han:SPRD rat model of PKD, treatment with rapamycin reduced kidney enlargement by 65%, cyst volume by more than 40%, and prevented the loss of kidney function when compared to animals not receiving rapamycin. A third new treatment scheduled for initiation in the near future uses the drug tolvaptan that inhibits cyst formation by blocking certain vasopressin receptors (VPV2R) in the kidney. In both a rat model and a mouse model of PKD, a tolvaptan-like drug inhibited renal cyst development and kidney enlargement, and in the mouse model it actually reversed cyst and kidney enlargement. Because tolvaptan interferes with water reabsorption by blocking the VPV2 receptors for vasopressin, thereby decreasing stimulation to cyclic AMP with its capacity to stimulate cyst formation, the possibility existed that simply increasing water intake might also simulate this effect and decrease cyst formation. This question was addressed in the PCK rat model of PKD in which high water intake was associated with a reduction in kidney size and improved renal function. This beneficial effect was associated with decreased renal expression of vasopressin (VPV2) receptors.

For references, please e-mail the editor.

Cleveland Clinic Participates in NIH-Funded ADPKD Study

Cleveland Clinic, in collaboration with Mayo Clinic, Tufts University-New England Medical Center, Beth Israel Deaconess Medical Center, Emory University, Kansas Medical Center, Washington University, and University of Colorado Health Sciences Center, has been funded by the NIH to participate in HALT-PKD, a 5-year, multi-center, double-blinded, interventional study of patients with ADPKD. The study is designed to determine if inhibition of the renin-angiotensin system will decrease the development of renal cysts and preserve GFR. There are two groups of patients. Group A includes patients 15-49 years old with a GFR >60mL/min/1.73 m². Group B includes patients 18-64 years old with a GFR 30-60 mL/min/1.73 m².

The study will compare the efficacy of treating ADPKD patients who have hypertension with an ACE-I/ARB drug combination versus an ACE-I with placebo. All study medications and testing, including kidney and cardiac MRI, serum chemistries, and 24-hour urine collections, are provided at no cost to participants.

Interested individuals should contact Robin Woltman, the Project Manager, at 314.362.1318 or visit the HALT PKD Web site: pkd.wustl.edu/pkdtn.
New Approaches to Assessing the Hypertensive Patient

Christopher Hebert, M.D.

The initial office evaluation of a hypertensive patient is an important opportunity to set the stage for successful management. National guidelines outline the basics, including ascertainment of cardiac risk factors, physical exam, basic laboratory tests and EKG. A more in-depth approach involves a thorough risk assessment, as well as tailoring of drug treatment to the individual. The components of an evaluation beyond the basics can be categorized into approaches that (1) assess blood pressure control, (2) estimate risk, and (3) predict response to pharmacologic interventions.

The best reflection of “true” blood pressure control is obtained with a 24-hour ambulatory blood pressure monitor (ABPM). This device, worn while the patient goes about his or her usual activities, obtains brachial blood pressure readings every 15 minutes during the day and every 30 minutes during sleep. The mean daytime systolic pressure obtained by 24 ABPM is perhaps the best single measure of true control. In addition, this test provides valuable information regarding nocturnal pressures. Nondipping (when nocturnal blood pressure fails to decrease by at least 10% of the daytime value) has been shown to be an independent marker of cardiovascular risk. For ongoing assessment of control, home measurement using a validated device is the best option. Office pressures alone have a lower correlation with cardiovascular risk.

Risk estimation in the hypertensive patient may be accomplished with a combination of statistical prediction tools and office-based diagnostic procedures.

After collecting the required data (demographics, past medical and social history, exam findings, basic laboratory tests and EKG) one can utilize published risk prediction tools to estimate the likelihood of heart disease, stroke and renovascular disease. The ratio of plasma aldosterone to renin can be used to estimate likelihood of aldosteronism, and published likelihood ratios can help.

Two notable office-based procedures include assessment of the ankle-brachial index (ABI) and measurement of vascular stiffness. The ABI is a sensitive test for peripheral arterial disease, which signifies elevated cardiovascular risk. Office devices are available to quickly and safely assess arterial stiffness. For example, a method using applanation tonometry of the radial artery allows analysis of the pulse waveform. The velocity of the waveform and the amount by which the wave reflected from the periphery augments the central aortic pressure can be estimated. In our office, assessment of vascular stiffness requires approximately five minutes of nurse time per patient, and provides important additional information regarding risk.

When recommending a medication, it may be useful to know which, among the many options, is most likely to effectively lower blood pressure for a particular individual. Mean decreases between age and race categories give some indication, but this approach is limited due to individual variation within groups. Another approach, plasma renin profiling, has proponents, but to date has not clearly been shown to be reliable. Perhaps the most promising approach is noninvasive hemodynamic profiling. Office devices for estimation of intravascular volume, vascular resistance, and cardiac output, along with expert clinicians, has been shown to achieve better blood pressure control than expert management alone.

Truly individualized care, therefore, involves accurate knowledge of the level of blood pressure control, the risks facing the patient, and predictions regarding which treatment is likely to be effective.
Identifying Risk for Rejection of Transplanted Kidneys

Emilio Poggio, M.D.

Kidney transplantation remains the best therapeutic option for patients suffering end-stage renal disease, providing patients better quantity and quality of life. However, organ shortage continues to be a major limitation and, therefore, prolonging the half-life of currently available transplanted kidneys is important.

Despite significant advances in the development of new immunosuppressive medications, the long-term success of kidney transplantation remains curtailed by graft failure due to immune-mediated injury to the transplanted organ. This injury cannot currently be fully predicted by routine laboratory testing. There is some evidence that the strength of the immunity against human organ transplants in general begins even before the actual time of transplantation, especially when patients are awaiting kidney transplantation during the dialysis treatment. For example, antibodies against common transplant antigens can be generated in patients with previous transplants, blood transfusions or through pregnancy. Similarly, the immune system could build up immunity to transplant antigens through infections or other medical events (by cross-reactivity) common to patients on dialysis treatment. As a result, all patients on the waiting list for a kidney transplant are routinely tested for such alloantibodies (humoral arm of the immune system) by the Panel of Reactive Alloantibodies, or PRA, test. The higher the number of pre-formed antibodies, the more difficult to find a matched organ with no antigens for the present antibodies.

Chart depicting the relationship between PRT positive or negative test (Figure A) with the presence of acute rejection. Figure B shows the same information but related to the PRA status.
Analogously, T cells (cellular arm of the immune system) can be present or developed while awaiting transplantation and could have a negative impact in the post-transplant period. Thus, early identification of patients with such allo-reactive T cells (lymphocytes reactive to transplant antigens) could be important for risk-stratification of patients. Knowing who is at high or low risk for cellular immune mediated transplant injury may allow for individualization of immunosuppressive therapy, thereby allowing more immunosuppression to those at high risk to avoid rejection and less to those who do not need it so to avoid side effects.

Along with Peter Heeger, M.D., from Mount Sinai Medical Center, New York, and Donald Hricik, M.D., and Joshua Augustine, M.D., from University Hospitals of Cleveland, we developed a test to detect these T cells reactive to transplant antigens analogous to the PRA test that detects antibodies to the same antigens. This test complements the already clinically available PRA test. We showed that the PRT assay provides complementary information to the PRA test and helps to identify high-risk kidney transplant candidates and thus predict post-transplant outcome.

We recently obtained NIH funding for a period of 5 years to further expand on these preliminary results and overcome the barriers to bring this promising biomarker tool to the bedside.

For references, please e-mail the editor.
News Affecting the Practice of Nephrology

Emil P. Paganini, M.D., F.A.C.P., F.R.C.P.

Appropriately Valuing Monthly Care of Patients on Dialysis

We have been working under the temporary codes set up by the Centers for Medicare and Medicaid Services (CMS) for our end-stage renal disease (ESRD) monthly care of patients on dialysis – the so-called “G” codes. These codes were established to capture the number of patient-physician interactions for the month and to assure a minimum of at least one “comprehensive” visit by the caregiver. While the term “comprehensive” has specific meanings in the Evaluation and Management (EM) coding system, the meaning here is specific to the ESRD patient’s needs and the caregiver’s need to address certain areas of care.

Having been arbitrarily established by CMS, what these codes represent is not clear. Thus CMS has asked that the codes be described and valued by the groups who are charged with this activity, specifically the Current Procedural Terminology (CPT) Committee and the Relative Values Update Committee (RUC) Committee of the AMA. As a consequence of this request, nephrologists will be asked to describe what the physician work involved in delivery of one full month’s ESRD care when the patient is seen by either the physician and/or his/her nurse practitioner/physician’ assistant.

This data will be collected by the RUC committee, which is being assisted by the Renal Physician’s Association (RPA). This latter group already has held regional meetings and done several mock surveys. The findings indicate that renal physicians tend to undervalue their activity and don’t relate all the activity rendered as much is considered “usual and customary” and, thus, are bundled into their other activities without recognizing the work value of that specific activity.

RPA is currently working with CMS as well as both AMA Committees (CPT and RUC) to better capture all the work involved in ESRD monthly care so that physician work can be valued appropriately. It is anticipated that a RUC survey will be generated in the fall of this year and used as the basis for this evaluation.

Rethinking Hemoglobin Limits

On another front, there has been a recent “Black Box Warning” placed on Erythropoietin type drugs. While based on data both from the ESRD field and the oncology field, implications of high hematocrit/hemoglobin targets have been outlined. This entire area is one of great debate and concern for all involved. Indeed, the National Kidney Foundation’s Kidney and Dialysis Outcome Quality Initiative (K-DOQI) has lowered its target to reflect the original package insert labeling and to underline the data outlined in the “Black Box.”

There are, however, many who believe that this limit is based upon flawed data and, thus, are concerned that currently stated hemoglobin limits may be an overreaction. The practitioner is therefore torn between new limits and altered practice, or continuing in their “usual and customary” way. The Renal Network (Network 9/10), which is responsible for quality oversight in the four-state area of Ohio, Kentucky, Indiana and Illinois, recently asked its Medical Review Board to address this issue and its most recent statement reflects a more cautious approach to the upper limit of hemoglobin both in the ESRD as well as the CKD stage 3-5 patients. The FDA will be addressing this issue during a series of meetings. For the present, however, it would be advised that an absolute upper limit of 12 gm of hemoglobin be practiced in your ESRD dialysis patients with a range from 10-12 gm of hemoglobin as the target range. The targets for the CKD population are not as clearly established.
End-stage renal disease (ESRD) is proliferating in the United States, fueled by epidemic diabetes and obesity, and, paradoxically, improved outcomes in cardiac disease such that more patients with hypertension and diabetes survive to develop kidney failure. Excellent outcomes from renal transplantation are limited by scarcity of donor organs, so that fewer than 20% of patients with kidney failure ever receive a transplant. (Based on Organ Procurement and Transplantation Network Data as of April 15, 2007.) The majority depends on hemodialysis and suffers extraordinary mortality and morbidity at great expense. Recent research has shown improved control of blood pressure, nutrition and cardiac disease with high-dose dialysis, but nationwide implantation of this strategy would overwhelm existing resources. Consequently, innovative efforts in tissue engineering and biomedical engineering strive to create alternatives to transplant and in-center dialysis.

The ideal alternative therapy should provide clearance, convenience and cost savings. Therefore, a technological quantum leap is required to implement the “three Rs” of twenty-first century healthcare in a solution for ESRD patients:

1. **Relocation** - the location of care must be relocated from the healthcare facility to the patient’s own home.

2. **Reduction** - there must be a significant reduction in disposables, which are expensive to purchase and expensive to discard.

3. **Reliability** - Monitoring and control of therapy must rely on integrated sensing and automated controls, rather than minute-to-minute monitoring by medical staff.

A wearable or implantable kidney integrated with the state-of-the-art electronics would certainly achieve the above characteristics.

Our group has focused on membrane technology as a limiting step in implantable or wearable therapy for ESRD because existing dialysis cartridges are physically large and require high pressures for blood circulation. Renal replacement therapy is implemented as an extracorporeal circuit rather than as an implanted device such as a pacemaker or AICD because of the limits of existing hollow-fiber polymer cartridges. The low hydraulic permeability of these devices – both in resistance to blood flow along the length of the hollow fiber and the driving force needed for ultrafiltration – create the need for mechanical pumps to move blood through the filter. The hydraulic permeability of the membranes is a function of the pore shape, size distributions and membrane thickness. Narrow pore size distributions improve discrimination between filtered and retained molecules and increase hydraulic permeability by allowing the mean pore size to approach the desired cutoff of the membrane; but pores in existing polymeric membranes typically have a broad size distribution and irregular features. The hydraulic permeability and hollow fiber geometry of existing membranes dictates a package size and pump requirement that preclude implantation.

An implantable membrane for blood separations such as dialysis or ultrafiltration would enable a paradigm shift in treatment of ESRD. In a recent pair of publications, our group has outlined the requirements for such a novel membrane, and our first steps in an implementation of such a membrane using silicon nanotechnology. Prototype membranes displayed high hydraulic permeability closely matching first-principles fluid mechanics predictions, and a barrier to albumin passage perfectly predicted by a classic steric-hindrance model. We are presently optimizing our membrane design for a next-generation renal replacement system.
Renal dysfunction has been shown to be a robust prognostic marker for cardiovascular morbidity and mortality in various patient populations. Post-operative renal dysfunction, even if defined as transient and mild, has been associated with higher mortality. In its severe form, acute renal failure requiring dialysis carries a 50% mortality tag in patients post open-heart surgery. The old dogma that patients die with rather than because of acute renal failure has been shaken in recent years, as it’s been shown that renal dysfunction contributes to worse outcome, and is not merely a marker of severity of illness.

There is wide variation in timing of renal consultation; it ranges from early to very late during the course of acute renal failure. It has been suggested that delayed recognition of renal dysfunction may lead to adverse consequences.

It is imperative that patients who are at high risk for perioperative renal injury be evaluated in a timely fashion. To that effect, the Department of Nephrology and Hypertension recently has established a clinic dedicated to the evaluation of patients at high risk for peri-procedure kidney injury/failure.

Propensity for renal injury is an interplay of a patient’s renal reserve, operative risk and perioperative complications. Moreover, the effects of the risk factors are additive.

Pre-existing kidney disease is a robust predictor of acute renal failure and residual renal function. Therefore, those with estimated glomerular filtration rate of less than 60 ml/min, and/or proteinuria should be considered at high risk for renal complications (see Figure).

Comprehensive renal care includes preoperative assessment and optimization of renal function, perioperative care, and post discharge follow-up.

Preoperative evaluation:

- Acquisition of renal history
- Imaging of kidney size/symmetry, and relative contribution and patency of renal arteries
- Accurate assessment of renal reserve:
  - Creatinine, estimated GFR (MDRD), Cystatin C, creatinine clearance, iothalamate GFR
  - Establishment of biomarker baseline levels
  - Stabilization of acute renal perturbations
  - Risk assessment
  - Enrollment in clinical trials for the prevention and treatment of acute renal failure
- Medication adjustments
- Blood pressure control
- Optimization of hematocrit levels
Perioperative renal impairment has been traditionally diagnosed with oliguria/anuria and an increase in serum creatinine. However, creatinine is an insensitive marker of renal functional impairment; glomerular filtration rate could be reduced by 50% without a change in creatinine level. The latter is due to increased creatinine secretion, and other compounding variables common in patients post surgery, such as volume loading (dilution) and muscle wasting (generation). Recently the focus has changed toward biomarkers that detect injury (acute kidney injury) from that which quantifies filtration function lost (acute renal failure).

**Perioperative care and follow-up:**
- Kidney injury molecule-1, neutrophil gelatinase associated lipocalin, and interleukin-18
- Early detection of renal injury
- Correction of pre-renal/post-renal states
- Monitoring of electrolytes
- Volume management
- Optimization of renal perfusion
- Recognition of renal emergencies
- Timely initiation of renal support
- Accurate assessment of residual function
- Responsive assessment of renal recovery, especially when maintained on dialysis
- Establish outpatient continuity of renal care

For an appointment with Dr. Demirjian for a risk assessment for one of your patients, please call 216.444.6771.
Diabetic nephropathy remains the most common cause of end-stage renal disease (ESRD) in the United States. Evidence from many clinical trials has proven convincingly that tight control of blood pressure and blood glucose, along with blockade of the renin-angiotensin-aldosterone system (RAAS), significantly ameliorates progressive CKD in patients with established diabetic kidney disease. Many diabetics at risk fail to reach recommended blood pressure and glycemic targets, this being cited as a major reason for the continued public health problem. However, even in idealized study populations with exquisite control of all modifiable factors in a structured highly monitored setting, the current “standard of care” treatment options for diabetic kidney disease at best slow the pace toward what seemingly is an inevitable decline in renal function. The loftier goal of arresting diabetic kidney disease in its tracks has remained elusive and is fertile ground for investigation.

In an effort to address this goal, attention has been paid to potential novel treatments for diabetic nephropathy that may complement the current standard of care. Animal studies have implicated a deficiency in the glycosaminoglycan (GAG; e.g., heparan sulfate) content of the glomerular basement membrane (GBM) from diabetic kidneys. In a high glucose milieu it has been shown that heparanase, an enzyme responsible for breakdown of heparan sulfate is significantly upregulated. Functionally, it is hypothesized that an acquired defect of GAG content, and thus a loss of net anionic charge of the GBM, is at least partially responsible for the defect in selective permeability that leads to albuminuria. Since abnormal GAG metabolism appears to play an important role in the development of functional abnormalities observed in diabetic nephropathy, it is logical to explore the possibility that restoration of normal GAG content in the GBM may ultimately be renoprotective by mechanisms independent of, but complementary to, current therapies.

Sulodexide is an agent compromised of predominantly heparan sulfate GAGs, and though in the same family as low-molecular weight heparin, has no anticoagulant properties in its oral dose range. With promising results from animal models, Sulodexide has been studied in pilot trials of patients with diabetic nephropathy. In patients with both Type 1 and Type 2 micro- or macroalbuminuric diabetic kidney disease already receiving RAAS blockade, significant reduction in albuminuria >50% were seen. What’s more interesting is that from the time of cessation of therapy, the reduced proteinuria was maintained for up to four months, suggesting that indeed restoration of what was a previously structurally abnormal GBM translated into a sustained improvement in its function despite drug withdrawal. Additionally, safety data from these preliminary studies is very favorable with a low incidence of reported side effects.

Cleveland Clinic and the Collaborative Study Group are currently involved in large, industry-sponsored multicenter trial studying the long term renoprotective effect of sulodexide in patients with established Type 2 diabetic kidney disease already on standard of care therapies. Eligible patients include those with controlled blood pressure on maximum tolerated RAAS blockade with elevated creatinine (males 1.5-3mg/dL, females 1.3-3mg/dL) and urine protein excretion > 900mg/24 hours. The primary endpoint of this randomized, placebo-controlled study is the composite of doubling of serum creatinine and/or ESRD. Enrollment is currently ongoing and approximately half of the planned 2,240 patients have already been randomized. If you have patients with established diabetic kidney disease who may qualify for this trial, please contact:

Brian Stephany, M.D., or Marc Pohl, M.D.  
Department of Nephrology and Hypertension  
216.444.5382  
stephab@ccf.org
Cleveland Clinic's Department of Nephrology and Hypertension has a long and proud tradition of training doctors to be specialists in the field of Nephrology and Hypertension. The specifics of how physicians are trained have changed dramatically over the years. First certified by the Accreditation Council for Graduate Medical Education (ACGME) in 1987, the Nephrology Fellowship program has continued to work with the ACGME to remain up-to-date with the latest and best tools for ensuring our graduates are among the best trained nephrologists in the world. Currently, we have six fellows per year in ACGME-approved 2-year training positions, and the option of having an additional year of training in Intensive Care Nephrology.

Our graduates have enjoyed moving on to many prominent academic medical centers and private practices, as well as subspecialty training in transplantation. Such well known places include: Brigham and Women's Hospital, University Hospitals of Cleveland, Mayo Clinic, Bay State Medical Center, and of course, our own department. Several graduates have stayed local and made significant contributions to the department and the profession.

From the early days to now, fellows and staff have been involved in research projects. Traditionally strong in the pathophysiology and management of hypertension, recent fellow research has enhanced our knowledge in the outcomes of kidney and pancreas transplantation as well as validating the techniques that estimate kidney function. Fellows are instructed in research design and conduct as well as experimental methods and biostatistics.

Nephrology and Hypertension currently ranks as the 4th most popular specialty program within internal medicine, behind Cardiology, Gastroenterology, and Hematology-Oncology, as ranked by number of applications. Cleveland Clinic received 222 applications for nephrology this past application year, which is above the national average of 181 applications per program. For this upcoming year, nephrology training programs across the United States will be utilizing the computerized match process to better assist in matching programs to qualified applicants. We look forward to another record year.
Clinical Trials
Department of Nephrology and Hypertension

Chronic Kidney Disease (CKD)

CRIC
Chronic Renal Insufficiency Cohort Study.
The goals of this study are to examine risk factors for CRI and CVD events among patients with varying severity of CRI and to develop predictive models that will identify high-risk subgroups. Status: Ongoing

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

HALT
Halt-PKD (Halt Progression of Polycystic Kidney Disease)
This is a large, randomized, clinical trial to determine the impact of intensive blockage of the renin-angiotensin-aldosterone system (RAAS) with a combination of angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin receptor blocker (ARB) drug therapies. Status: Enrolling

Rapamune®
Pilot Study of Rapamycin as Treatment for Autosomal Dominant Polycystic Kidney Disease (ADPKD).
This study is a prospective, randomized, placebo-controlled, clinical trial designed to compare the effects of an agent that has antiproliferative (1,2), anti-angiogenesis (3), and tumor-progression blocking capabilities (4), namely, rapamycin (Rapamune®), in the treatment of autosomal-dominant polycystic kidney disease (ADPKD). Status: Enrolling

Renal Transplant

MYGAIN
This four-week, multi-center, randomized, prospective, double-blind, parallel-group study will investigate the safety and tolerability of converting kidney transplant recipients with mild, moderate or severe GI symptoms who are MMF in combination with a calcineurin inhibitor (cyclosporin, USP or tacrolimus) with or without steroids, to an equimolar dose of myfortic. Status: Enrolling

CTOT
Noninvasive Monitoring to Predict Outcome in de novo Kidney Transplant Recipients.
The object of this observational study is to determine whether any single test, or a combination of tests, obtained during the first six months after transplantation is associated with the absence of the composite endpoint at six months (i.e., clinically evident acute rejection, subclinical injury, graft loss or death), identifying low risk patients. Status: Enrolling

Living Donor
The Long-term Medical and Psychosocial Implications of Becoming a Living Kidney Donor: a Canadian Prospective Pilot Study.
The purpose of this study is to compare living donors with eligible non-donors on their one year change in many renal physiological measurements (such as blood pressure, proteinuria, and predicted glomerular filtration rate), potential emerging risk factors for cardiovascular disease, end-stage renal disease and death. Status: Enrolling

ICU studies

Evolve
The purpose of this study is to test whether single or serial measurements of plasma NGAL (or other biomarkers) obtained in the immediate post-op period will aid in the early diagnosis of acute kidney injury. Status: Enrolling

VA
The VA Cooperative study is a multicenter (24 VA sites and seven non-VA sites), parallel group trial of two strategies for the management of renal support in ARF secondary to acute tubular necrosis in critically ill patients. Status: Ongoing

Quark
The purpose of this study is to determine the safety and dose-limiting toxicities (DLTs) of 15 NP when administered as a single IV injection (10-20 ml/min) for the prevention of acute kidney injury (AKI) in high-risk patients undergoing major cardiovascular surgery. Status: Enrolling

AVERT
The purpose of this double-blind, placebo-controlled trial is to evaluate Aranesp® (darbepoetin alfa) for the prevention of acute kidney injury (AKI) in high-risk patients undergoing open heart surgery (AVERT). Status: Enrolling

Outpatient Dialysis Studies

Advance
The purpose of this randomized study is to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in subjects with chronic kidney disease (CKD) who are receiving hemodialysis. Status: Enrolling

ASA
This pilot study will determine if the Ultegra assay can be reliably used in the dialysis population to assess the antiplatelet effect of different aspirin doses in this population. Status: Enrolling

PRT
This is a prospective observational analysis of peripheral blood T-cell immune reactivity in potential transplant candidates. Status: Enrolling
Selected Publications from the Department of Nephrology and Hypertension


William Fissell, M.D., will be caring for patients who require dialysis while in the intensive care unit. Dr. Fissell earned his medical degree from Case Western Reserve University School of Medicine. He finished an internship and residency at University Hospitals of Cleveland. Dr. Fissell completed a fellowship at University of Michigan Health Systems in Ann Arbor. At Cleveland Clinic, he is joint-appointed in the departments of Nephrology and Hypertension and Biomedical Engineering.

Christopher Hebert, M.D., will see patients with resistant hypertension. Dr. Hebert graduated from The Ohio State University College of Medicine and Public Health in Columbus. He completed a residency at the University of Cincinnati Medical Center and University Hospitals. He also completed fellowship at the VA Medical Center in Cleveland. Dr. Hebert is appointed in the Department of Nephrology and Hypertension as well as Quantitative Health Sciences at Cleveland Clinic.

Priya Kalahasti, M.D., specializes in end-stage renal disease. Dr. Kalahasti received her medical degree from Sri Venkatesvara University Medical College in Tirupati, India. She completed her residency, internship and fellowship at Cleveland Clinic.
Martin Lascano, M.D., specializes in dialysis in a hospital setting. Dr. Lascano received his medical degree from Universidad Del Valle-Division de Ciencias de la Salud in Colombia. He completed his residency, internship and fellowship at Cleveland Clinic.

Mohammed A. Rafey, M.D., M.S., will see patients with hypertension. Dr. Rafey received his medical degree from Bangalore University in India and his Master of Science (Clinical Research) degree from New York University. He completed an internship and residency in internal medicine at North General Hospital in New York. He completed fellowships in both hypertension and nephrology at Mount Sinai Hospital in New York. Dr. Rafey’s most recent position was Clinical Associate in the Department of Medicine at Mount Sinai Hospital in New York, where he was also an instructor of medicine (nephrology).

James F. Simon, M.D., will specialize in the treatment of kidney stones, chronic kidney disease and hypertension. He earned his medical degree from Loyola University in Chicago and completed a residency in internal medicine at Brooke Army Medical Center at Fort Sam in Houston. Dr. Simon also held a fellowship at Walter Reed Medical Center in Washington, D.C. Most recently, he served as Chief of Nephrology Service, Medical Director of the Infusion Clinic and Medical Director of the Hemodialysis Unit at Brooke Army Medical Center.
Department of Nephrology and Hypertension

Staff Directory

Martin Schreiber, Jr., M.D.
Chairman, Department of Nephrology and Hypertension
Phone: 216.444.6365
Specialty interests: Chronic kidney disease, diabetic nephropathy, acute and chronic dialytic therapies, continuous ambulatory peritoneal dialysis (CAPD), dialysis complications, cardiorenal syndrome

William E. Braun, M.D.
Phone: 216.444.6995
Specialty interests: Medical renal transplantation (immunosuppression, rejection, and complications), autosomal polycystic kidney disease (ADPKD) glomerulonephritis, chronic kidney disease after non-renal organ transplantation, hypertension

Emmanuel L. Bravo, M.D.
Phone: 216.444.5829
Specialty interests: Molecular cardiology, cardiovascular biology, endocrine and hypertension research, disorders of the renin-angiotensin-aldosterone system, pheochromocytoma, mineralocorticoic disorders

Sevag Demirjian, M.D.
Phone: 216.445.7586
Specialty interests: Acute renal failure, renal replacement therapy, chronic kidney disease (CKD) epidemiology, genetics in kidney disease, hypertension

Richard Fatica, M.D.
Phone: 216.445.9953
Specialty interests: Fellowship education and training program, kidney and pancreas transplantation, dialysis, hypercoagulable states in chronic kidney disease, calcium and phosphate disorders

Phillip M. Hall, M.D.
Phone: 216.444.6777
Specialty interests: Residency training program, renal disease progression, screening techniques for assessing renal anatomy and function, evaluation of glomerular filtration and renal plasma flow, renal calculi, systemic and regional hemodynamics of hypertension, hypertension in special populations, lupus nephritis
Robert J. Heyka, M.D.  
Phone: 216.444.8895  
Specialty interests: Acute, continuous renal replacement therapy, hemodialysis, evaluation of adequacy in dialysis modalities, unique aspects of treating hypertension and other disorders in the chronic dialysis patient, renal failure in the ICU patient and those with multiple, severe cardiovascular risk factors.

Joseph V. Nally, Jr., M.D.  
Phone: 216.444.8897  
Specialty interests: Comprehensive care of the chronic kidney disease (CKD) patient, resistant hypertension, diagnosis and detection of renovascular hypertension, renal physiology and microvasculature, polycystic kidney disease, prevention of renal dysfunction in diabetic patients, screening for cardiovascular disease in end-stage renal disease patients, and medical renal transplantation.

Saul Nurko, M.D.  
Phone: 216.445.8628  
Specialty interests: Anemia of chronic kidney disease, iron metabolism in health and disease, acute and chronic renal failure, dialysis, ICU nephrology, transplantation, renal calculi, glomerulonephritis.

Emilio Poggio, M.D.  
Phone: 216.444.5383  
Specialty interests: Kidney and pancreas transplantation, chronic kidney disease in solid organ transplantation, chronic kidney disease, evaluation of renal function.

Mark A. Pohl, M.D.  
Phone: 216.444.6776  

Brian Stephany, M.D.  
Phone: 216.444.5382  
Specialty interests: Chronic kidney disease, general chronic kidney disease after non-renal solid organ transplant, kidney transplantation, glomerular disease.

Emil P. Paganini, M.D., F.A.C.P.  
Phone: 216.444.5792  
Specialty interests: Hemodialysis, hemofiltration, hemoperfusion, ultrafiltration techniques, membrane pheresis, continuous replacement therapy, membrane effects on cellular function in the uremic patient, physiology of acute and chronic renal failure: prophylactic maneuvers for acute renal failure, geriatric ICU nephrology, osseous and hematological disturbances in chronic renal dysfunction, physiology and hemodynamic effects of r-huepo in patients with renal failure.

Qingyu Wu, M.D., Ph.D.  
Phone: 216.444.4351  
Specialty interest: molecular mechanisms in cardiovascular diseases.
Cleveland Clinic Excels in Latest
U.S. News Rankings

Kidney disease ranked No. 5 in the nation

The Cleveland Clinic Glickman Urological and Kidney Institute’s kidney disease program was ranked among the top 5 kidney disease programs in the United States by *U.S. News & World Report*.

The 2007 “America’s Best Hospitals” survey recognized Cleveland Clinic as one of the nation’s best hospitals overall, ranking the hospital as No. 4 in the country. Cleveland Clinic ranked in all 16 specialties surveyed by the magazine. Twelve of its specialties were listed among the top 10 in the United States. All Cleveland Clinic specialties placed in the nation’s top 20. For details, visit clevelandclinic.org.

Outcomes Data Available

The latest edition of outcomes data from the Cleveland Clinic Department of Nephrology and Hypertension is available. Our outcomes booklet also offers summary reviews of medical trends and approaches. Charts, graphs and data illustrate the scope and volume of services performed in our department each year. To view outcomes booklets for the Department of Nephrology and Hypertension as well as many other Cleveland Clinic medical and surgical disciplines, visit clevelandclinic.org/quality.