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Medicare's new Conditions for Coverage for dialysis facilities will require much from kidney specialists. Will your unit feel swamped by the data entry and other requirements? For more on dialysis, see our special section starting on p. 11.

Study Urges Early Diagnosis of CKD in Children

Increasing efforts are being made to prevent and treat chronic kidney disease (CKD) in children, before serious complications develop during adolescence and adulthood. One recent research endeavor has focused on characterizing proteinuria in children.

By assessing this condition, which is a hallmark of kidney dysfunction, investigators hope to not only slow the progression of CKD in children, but also to find new insights into disease progression that might be used to develop novel treatments for all kidney patients—adults and children.

Proteinuria and kidney disease

"We know that the severity of kidney disease tends to be associated with the amount and the duration of proteinuria," said Craig Wong, MD, of the University of New Mexico, in Albuquerque. "Therefore, persistent high grade proteinuria usually warrants a prompt evaluation for other symptoms of kidney dysfunction."

Most patients with proteinuria have no signs or symptoms, so the proteinuria is often discovered at a late stage. As a result, the distribution of proteinuria in young patients with poor kidney function is unknown.

To gain insights into the distribution of proteinuria and to identify characteristics associated with proteinuria in children, Wong and his colleagues look at a large group of children with mild to moderate kidney disease in the April *Clinical Journal of the American Society of Nephrology.*

The goal of their analysis of data from the Chronic Kidney Disease in Children (CKiD) study was to pinpoint potential environmental influences and to identify differences

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Home Hemodialysis Industry Poised for Growth

The market for home-based hemodialysis is growing and is poised to expand, nephrologists and industry representatives reported. Changes required by the Medicare Improvements for Patients and Providers Act (MIPPA), the Centers for Medicare and Medicaid Services (CMS), and a trend toward home health care may all help shift the winds in favor of home dialysis.

Currently limiting dialysis in the home are Medicare reimbursement levels, reimbursement for training, and the ability of patients and caregivers to perform the tasks necessary for the hemodialysis. But several factors are converging to encourage more home dialysis. For example, many patients still don't know about home dialysis as an option, but MIPPA and the CMS's new Conditions for Coverage now require that patients be informed of all the modalities for treating kidney damage, including home dialysis.

About one percent of dialysis patients are now dialyzing at home, said Christopher R. Blagg, MD, professor emeritus of medicine at the University of Washington, and a pioneer and supporter of home dialysis since the 1960s.

The total number of home hemodialysis patients in the United States is about 4000 currently, compared with roughly1000 in 2005, said Joe Turk, senior vice president of commercial operations for NxStage, which manufactures the most frequently used home dialysis machine.

That number is set to change. With the number of all dialysis patients in the United States growing 2 to 3 percent per year, "by 2020, it's estimated that about 800,000 people with kidney disease will

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in groups among children with chronic kidney disease.

Wong and his team studied data from more than 400 children one to 16 years of age who were enrolled in the CKiD study and were seen at 43 pediatric nephrology centers across North America.

"This study provides new information pertaining to the importance of proteinuria and factors associated with its development in the largest group of children with chronic kidney disease ever studied," said Wong. He added that the study has defined some of the risk factors for kidney disease progression and may help researchers design new and potentially therapeutic interventions to maintain patients' kidney function.

Identifying proteinuria in children earlier could help physicians slow or prevent kidney function loss at an early stage. For example, treatments such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers—so-called renin-angiotensin system (RAS) antagonists—could be prescribed to reduce proteinuria and slow kidney disease progression.

The investigators found that the level of proteinuria in children tended to be higher as their glomerular filtration rate decreased. Proteinuria also was associated with race. Non-Caucasian patients were more likely to have proteinuria than Caucasians, which suggests that differences in proteinuria might be related to genetic or environmental factors in some cases.

Proteinuria also was associated with glomerular causes of chronic kidney disease. Among the patients with glomerular causes of chronic kidney disease, those who took RAS antagonists tended to have lower levels of proteinuria compared with those who did not take the drugs.

"The likelihood that agents designed to affect the RAS system will protect renal function in children with chronic kidney disease, particularly those with glomerular causes of chronic kidney disease, is strengthened by this report," said John Mahan, MD, program director of the Pediatric Residency Program and the Pediatric Nephrology Fellowship Program at Ohio State University in Columbus. "These data should encourage all pediatric nephrologists to aggressively approach treatments that affect the RAS in children with chronic kidney disease."

According to William E. Smoyer, MD, director of the Center for Clinical and Translational Research at the Research Institute at Nationwide Children's Hospital in Columbus, Ohio, "This very large pediatric study confirms the importance of proteinuria as a highly relevant marker of kidney injury in children, as well as a predictor of future loss of renal function. Given the known role of proteinuria in inducing kidney inflammation and scarring, it also highlights the important benefits of treatment of chronic glomerular proteinuria with renin-angiotensin system antagonists."

The study's results could encourage other investigators to develop novel therapies that target the RAS system, Smoyer said.

The CKiD study was established by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), in collaboration with the National Institute of Neurological Disorders and Stroke and the National Institute of Child Health and Human Development [Furth SL, Cole SR, Moxey-Mims M, et al.: *Clin J Am Soc Nephrol* 2006; 1(5):1006–1015].

Patients enrolled in the study undergo annual physical examinations that document characteristics such as height, weight, and blood pressure. Cognitive function, quality of life, nutritional, and behavioral questionnaires are also completed; glomerular filtration rates are measured; and samples of serum, plasma, urine, hair, and fingernail clippings are stored.

A number of analyses are being made with data from the CKiD study. Researchers hope to determine risk factors for progression of pediatric chronic kidney disease, to examine the impact of chronic kidney disease on neurocognitive development, to understand the impact of chronic kidney disease on risk factors for cardiovascular disease, and to learn about the impact of chronic kidney disease on growth.

"The CKiD study offers pediatric nephrologists an unprecedented opportunity to identify potentially modifiable factors that may enable them to reduce the progressive loss of kidney function in children and improve their quality of life," said Smoyer.

Conducting such analyses is important because the incidence of end stage renal disease in children in the United States is 14.4 per million people, according to the 2008 U.S. Renal Data System's Annual Data Report.

"The life expectancy of children with end stage renal disease is markedly compromised," said Wong. "Thus, any infor-

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Journal View

Benazepril-Amlodipine Reduces Cardiovascular Risk in High-Risk Patients

For high-risk patients with hypertension, benazepril plus amlodipine offers greater protection against cardiovascular events than benazepril-hydrochlorothiazide—despite similar effects on blood pressure, according to a report in *The New England Journal of Medicine*.

The industry-funded ACCOMPLISH trial included 11,506 patients with hypertension with a history of or risk factors for cardiovascular events. One group received the angiotensin-converting enzyme inhibitor benazepril plus the calcium-channel blocker amlodipine. The other group received benazepril plus the thiazide diuretic hydrochlorothiazide. Patients were followed up for a composite endpoint of cardiovascular death, nonfatal myocardial infarction or stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization.

The study was stopped early after 36 months. There was no more than a 1 mm Hg difference in systolic blood pressure between groups. However, the primary outcome rate was 9.6 percent with benazepril-amlodipine versus 11.8 percent with benazepril-hydrochlorothiazide, with a hazard ratio of 0.80. The benazepril-amlodipine group had a similar reduction in a composite endpoint of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

The results add to the evidence that benazepril-amlodipine combination can protect against end-organ damage, independent of the effect on blood pressure. "[O]ur findings may increase the options for combination treatment to reduce the risk of cardiovascular events among patients with hypertension," the ACCOMPLISH investigators concluded [Jamerson K, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V, Hester A, Gupte J, Gatlin M, and Velazquez EJ, for the ACCOMPLISH Trial Investigators: Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008; 359:2417–2428].

Endothelin Antagonist Reduces Albuminuria in Diabetic Nephropathy

Treatment with the endothelin A-selective antagonist avosentan can reduce urinary albumin excretion in diabetic patients with macroalbuminuria, concludes a trial in the *Journal of the American Society of Nephrology*.

The Endothelin Antagonist Evaluation in Diabetic Nephropathy Study included 286 patients with diabetic nephropathy at 58 European centers. All had macroalbuminuria, with a urinary albumin excretion rate (UAER) of 0.2 to 5.6 mg/min, and blood pressure of less than 180/110 mm Hg. In addition to standard angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker therapy, patients were randomly assigned to 12 weeks of treatment with avosentan, 5 to 50 mg, or placebo.

All avosentan dosage groups had reductions in UAER: from 16 to 30 percent, compared with a 36 percent increase in the placebo group. Median relative reductions in UAER were 29 to 45 percent with avosentan, compared to a 12 percent increase with placebo. Creatinine clearance and blood pressure were unaffected. Peripheral edema occurred mainly at avosentan doses of 25 mg or higher; the rate of adverse events leading to treatment discontinuation was 7 percent.

Studies in rats suggest that endothelin antagonists can reduce inflammation, renal fibrosis, and albumin excretion. Adding avosentan to standard therapy can reduce albumin excretion in patients with advanced diabetic nephropathy, this industry-sponsored study reports. Larger confirmatory trials are needed, including data on the optimal avosentan dosage and long-term benefits of treatment [Wenzel RR, Littke T, Kuranoff S, Jürgens C, Bruck H, Ritz E, Philipp T, and Mitchell A, for the SPP301 (Avosentan) Endothelin Antagonist Evaluation in Diabetic Nephropathy Study investigators. Avosentan reduces albumin excretion in diabetics with macroalbuminuria. *J Am Soc Nephrol* 2009; 20:655–664].

Good Outcomes with Sirolimus Combinations in High-Risk Transplant Recipients

Sirolimus, given with either tacrolimus or cyclosporine, provides good one-year efficacy in high-risk renal allograft recipients, reports a trial in *Transplantation*.

The randomized, open-label, multicenter trial included 448 renal allograft recipients with risk factors for rejection: black race, nonprimary transplant, or high panel-reactive antibodies. They were assigned to sirolimus plus tacrolimus or sirolimus plus cyclosporine.

One-year efficacy failure rates were 22 percent with sirolimus-tacrolimus and 23 percent with sirolimus-cyclosporine. Acute rejection rates were 14 percent and 17 percent, respectively; graft survival was 90 percent in both groups. In patients receiving their assigned therapy, the glomerular filtration rate tended to be higher with sirolimus-tacrolimus.

Other one-year outcomes were similar between groups. Sirolimus-tacrolimus was associated with higher rates of diarrhea and herpes simplex. Other adverse events were more frequent with sirolimus-cyclosporine, including hypertension, calcineurin inhibitor toxicity, and increased creatinine.

It has been difficult to perform randomized trials evaluating outcomes in high-risk renal allograft recipients. This industry-sponsored study shows "equivalent benefit or risk" with the two sirolimus combinations studied, with no clear advantage of one regimen over the other [Gaber AO, Kahan BD, Van Buren C, Schulman SL, Scarola J, and Neylan JF, for the Sirolimus High-Risk Study Group: Comparison of sirolimus plus tacrolimus versus sirolimus plus cyclosporine in high-risk renal allograft recipients: results from an open-label, randomized trial. *Transplantation* 2008; 86:1187–1195].

CKD Awareness Is Rising, but Remains Low

Despite efforts to increase awareness, a large majority of Americans with chronic kidney disease (CKD) are still unaware of their disease, reports a study in the *Archives of Internal Medicine*.

Led by Laura C. Plantinga, ScM, of Johns Hopkins Bloomberg School of Public Health, Baltimore, the study included 2992 adults with stage 1 to 4 CKD from the National Health and Nutrition Examination Survey, 1999–2004. Patients were asked whether they had ever been told they had "weak or failing kidneys."

Awareness of CKD increased during the study period only in patients with stage 3 disease: from 4.7 percent in 1999–2000 to 9.2 percent in 2003–04. For patients with stage 1 or 2 CKD, the rate of awareness was about half of that for those in stage 3. Even in stage 4, less than half of respondents were aware of their CKD.

Factors associated with awareness were assessed in 1314 patients with stage 3 CKD. Those with proteinuria or hypertension were about three times more likely to be aware of their disease. Rates of awareness were twice as high for diabetics and for males. Awareness was unrelated to having a regular site for health care, educational attainment, insurance status, or obesity.

Recent guidelines have emphasized the need for early detection and prevention of CKD. The new results suggest that awareness of stage 3 CKD has nearly doubled in recent years, but remains low. The authors urge more aggressive targeting of groups with low awareness of CKD, including older patients, women, and patients without diabetes or hypertension [Plantinga LC, Boulware LE, Coresh J, Stevens LA, Miller ER III, Saran R, Messer KL, Levey AS, and Powe NR: Patient awareness of chronic kidney disease: trends and predictors. *Arch Intern Med* 2008; 168:2268–2275].

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mation that can ultimately contribute to decreasing the progressive impairment of kidney function in those with chronic kidney disease or lessen the morbidity associated with the disorder is extremely important to the health of children."

In addition to Wong's research, other investigations based on data from the CKiD study have uncovered useful information about kidney disease in children. One recent analysis found that hemoglobin declines as glomerular filtration rate decreases in these patients. These results indicate that clinicians should be mindful of the potential for hemoglobin decline and anemia even at early stages of chronic kidney disease [Fadrowski J, Pierce CB, Cole SR, et al.: *Clin J Am Soc Nephrol* 2008; 3(2):457–462].

Another project has characterized the distribution of blood pressure and the prevalence and risk factors for hypertension in pediatric chronic kidney disease patients. Researchers found that characteristics associated with elevated blood pressure included black race, shorter duration of chronic kidney disease, absence of antihypertensive medication use, and elevated serum potassium [Flynn JT, Mitsnefes M, Pierce C, et al.: *Hypertension* 2008; 52(4):631–637].

Such research efforts will help shape the future of kidney disease care in the United States. "Challenges for these and other investigators in the future are to design studies that directly engage in manipulation of modifiable factors such as RAS interventions, diet, body mass index, and other therapies to promote best retention of renal function in children with chronic kidney disease," Mahan said.