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COVID-19–Related AKI in Hospitalized Children

COVID-19 created a worldwide health, social, and economic crisis. Patients with COVID-19 usually present with respiratory and gastrointestinal symptoms, but severe cases can progress to a systemic disease affecting nearly all major organs.

Acute kidney injury (AKI) is a common complication of COVID-19 and, according to **Jameela Abdulaziz Kari, MD,** and colleagues, the pathophysiology of AKI in COVID-19 is multifactorial. The direct viral causes of AKI in COVID-19 are thought to be direct viral injury, dysregulated inflammation with cytokine storm, and vascular injury. However, the authors noted that other factors seen in similar diseases have been identified, including hypovolemia, heart failure (both left and right), sepsis, and dehydration.

There are few data available on the precise prevalence of AKI in patients with COVID-19. Reported estimates of AKI prevalence range from 19% to 46%, and as high as 68% of all critical care patients, with 20% of admitted patients requiring renal replacement therapy (RRT).

There are also variations in the reported epidemiology of AKI in children infected with SARS-CoV-2. Previous studies reported a strong association between AKI and Multisystem Inflammatory Syndrome in Children (MIS-C), a severe form of COVID-19 presentation that commonly occurs a few weeks following the initial, usually milder, symptoms.

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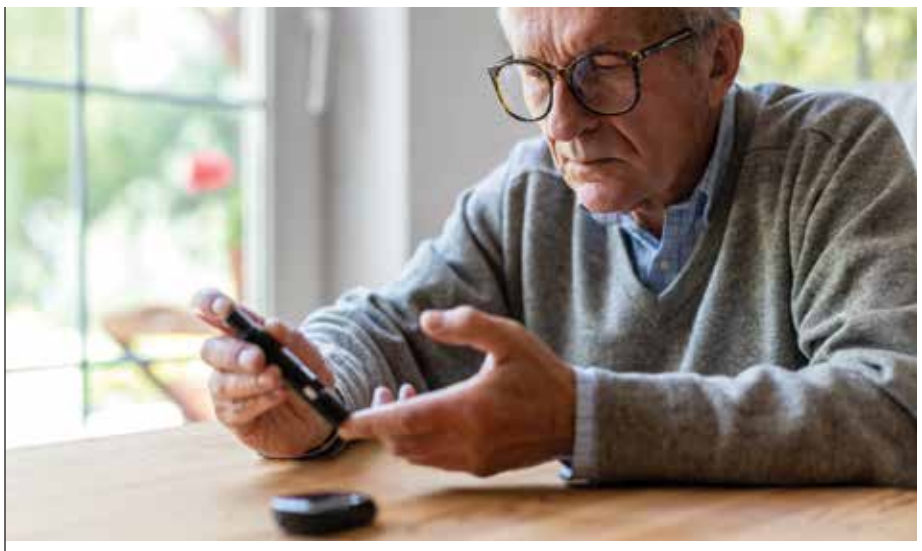

Risk of Six Cardiovascular Morbidities in Patients with Diabetes Mellitus and CKD

Patients with diabetes mellitus commonly develop chronic kidney disease (CKD). The age-standardized prevalence of diabetic kidney disease (DKD) according to results of a survey from the Global Burden of Disease report was 15 to 16 per 1000. A recent systematic review found that 31.3% of patients with incident end-stage kidney disease (ESKD) had diabetic nephropathy, and the

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Metabolic Acidosis and Adverse Renal Outcomes and Mortality

Chronic kidney disease (CKD) presents a major public health problem, with approximately 14% of the population diagnosed with CKD, with many progressing to end-stage kidney disease (ESKD) requiring initiation of dialysis or kidney transplantation. Among patients with CKD, the mortality rate is more than double that of the general population.

Patients with advanced CKD commonly develop metabolic acidosis due to a combination of dietary and metabolic acid load and diminished net acid excretion. Patients with CKD and metabolic acidosis are at risk for adverse outcomes, including progressive CKD, cardiovascular events, impaired immune response, bone and muscle loss, and death.

Studies designed to examine the association of metabolic acidosis with adverse renal outcomes have had conflicting results. In some observational studies there was an association between serum bicarbonate and progression of CKD (defined as ESKD requiring dialysis or transplant), a reduction of 50% in estimated glomerular filtration rate (eGFR), or reaching an eGFR of <15 mL/min/1.73 m^2. However, in other studies there was no association following adjustment for baseline eGFR.

Navdeep Tangri, MD, and colleagues conducted an observational, longitudinal, retrospective cohort study to determine whether metabolic acidosis is an independent risk factor for adverse renal outcomes and death, and to quantify the magnitude of its effect.

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Treatment of CKD-Associated Pruritus: A New FDA-Approved Treatment

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The approval by the US FDA on August 23, 2021, of difelikefalin (marketed as Korsuva™ by Cara Therapeutics) is a major step in improving the lives of patients on dialysis who suffer itching. CKD-associated pruritus (CKD-aP) is experienced by about 40% to 60% of patients with end-stage kidney disease.[1] Severe disabling itching occurs in about 20% and is associated with reduced quality of life, including sleep disorder and depression.

Difelikefalin is not the only "kid on the block" for treating CKD-aP, but it is the now the only FDA-approved treatment. The neuromodulators gabapentin and pregablin have been used with some success; however, they are associated with drowsiness, dizziness, and somnolence. Other agents, such as cannabinoids (the endocannabinoid palmitoylethanolamide), the κ-opioid-receptor antagonist nalfurafine hydrochloride, and phototherapy, have also been used but with varying degrees of success (great reviews by Combs et al[2] and Westby et al[3] are worth reading).

Difelikefalin is a major advance in treatment because it is a first-in-class kappa opioid receptor agonist that activates kappa opioid receptors on both peripheral neurons and immune cells. Thus, difelikefalin reduces the transmission of pain signals and the release of nerve sensitizing proinflammatory mediators including prostaglandins.[4] Because difelikefalin is peripherally active, it is not associated with central side effects such as sedation, dysphoria or sense of unease, and hallucinations.

The approval of difelikefalin is based on the results of two phase 3 trials: KALM-1 and KALM-2. The first of these two trials, KALM-1, was published in *The New England Journal of Medicine* by Fishbane and colleagues[5] and reflects US data. A global study, KALM-2, similarly designed and with similar results, was presented at ASN Kidney Week in 2020.[6]

KALM-1 was a double-blind, placebo-controlled, randomized trial in which patients on hemodialysis with moderate-to-severe pruritus received either difelikefalin 0.5 mcg/kg or placebo. Pruritus was evaluated by administering the 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS). The primary outcome was the proportion of patients with a 3-point or greater improvement in WI-NRS score from baseline to week 12. The trial showed a significant improvement in difelikefalin treated patients compared with those receiving placebo (49.1% vs 27.9%; $P<.001$). The proportion of patients achieving a 4-point or greater improvement in WI-NRS score was also significantly higher in the difelikefalin group compared with placebo (37.1% vs 17.9%; $P<.001$). Additionally, patients treated with difelikefalin reported a significant improvement in itch-related quality of life as assessed by the 5-D itch scale and Skindex-10 scale. Although adverse events were more common among the difelikefalin-treated patients compared with placebo (68.8% vs 62.2%), they were mild to moderate and limited in duration. The most common symptoms in the difelikefalin treated patients were diarrhea, dizziness, and vomiting.

KALM-1 was a well-conducted trial that showed efficacy over a short time window of 12 weeks. Other data on difelikefalin suggest a low potential for abuse (and relatedly no detectable activity at mu or delta opioid receptors, which have been associated with dependency).

In summary, we now have an approved treatment for CKD-associated pruritus that is rapidly effective and well tolerated. While difelikefalin currently needs to be administered parentarally after dialysis, an oral preparation is being developed. Difelikefalin is also being tested in the non-dialysis CKD population (ClinicalTrials.gov number, NCT03617536). Finally, dialysis patients with disabling itching have something to celebrate! ■

Dr. Singh reports no conflicts of interest related to difelikefalin or any other agents used in the treatment of CKD-associated pruritus.

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Risk of Six Cardiovascular Morbidities

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annual incidence of ESKD among diabetic patients increased approximately threefold over 2 decades.

Approximately 20% to 40% of patients with diabetes mellitus have DKD, resulting in a high risk of cardiovascular events. However, the risk and timing of the development of cardiovascular disease may differ depending on their type. According to **Chia-Ter Chao, MD, PhD,** and colleagues at the National Taiwan University Hospital, Taipei, Taiwan, there are few data available on whether CKD has differing influences on the risk of developing each cardiovascular morbidity in patients with newly diagnosed diabetes mellitus.

The researchers conducted an analysis of data from the Longitudinal Cohort of Diabetes Patients (LCDP) cohort to examine the risk trajectory of developing a wide spectrum of cardiovascular complications, i.e., heart failure, acute myocardial infarction (AMI), peripheral vascular disease (PVD), ischemic stroke (IS), hemorrhagic stroke (HS), and atrial fibrillation. Mortality was also an outcome of interest. Results of the analysis were reported online in *Cardiovascular Diabetology* [2021;doi.org/10.1186/s12933-021-01279-6.

Patients in the LCDP cohort diagnosed with incident diabetes mellitus between 2004 and 2010 were identified. Patients who developed CKD following diabetes diagnosis were matched with counterparts who did not develop CKD. The researchers examined the cardiovascular morbidity-free rates of patients in the two groups (with and without CKD) and conducted Cox proportional hazard regression analyses. The cumulative risk of developing each outcome consecutively during the study period was also assessed. Patients were followed-up until death, the development of any of the cardiovascular morbidities of interest, or the end of the study (December 31, 2011).

The study selection process began with 840,000 patients with diabetes mellitus in the LCDP cohort. Adults with incident diabetes mellitus and adequate follow-up time without any of the cardiovascular morbidities of interest were identified (n=429,616; 51.1%). Of those, 57,304 (13.3%) had CKD. Following 1:1 propensity matching, the final study cohort included 55,961 patients with DKD and 55,961 without DKD.

There were no significant differences between the two groups in demographic profiles, lifestyle factors, year of diabetes mellitus diagnosis, and most comorbidities and medications, with the exception of a modestly increased prevalence of chronic liver disease, gout, and malignancy in the group without DKD. The standard mean deviations of each variable between groups were lower than 0.1, suggesting that the distribution of each variable between groups was balanced.

Following a median of 4.2 years of follow-up, 11% of patients died (n=12,270), and 2.5% (n=2778), 1.1% (n=1250), 0.5% (n=534), 2.6% (n=2914), 0.7% (n=800), and 1.9% (n=2181) developed incident heart failure, AMI, PVD, IS, HS, and atrial fibrillation, respectively. Patients in the DKD group had a significantly higher incidence of developing heart failure ($P<.01$), AMI ($P=.04$), and PVD ($P<.01$), compared with patients in the group without DKD; there was no difference in the incidence of IS and HS between the two groups.

Results of Cox proportional hazard regression demonstrated that patients with diabetes mellitus and incident CKD had a significantly higher risk of morality (hazard ratio [HR], 1.1; 95% confidence interval [CI], 1.06-1.14), developing HF (HR, 1.282; 95% CI, 1.19-1.38), AMI (HR, 1.16; 95% CI, 1.04-1.3), and PVD (HR, 1.277; 95% CI, 1.08-1.52), compared with patients without CKD during follow-up. There were no differences in the risk of IS, HS, and atrial fibrillation between the two groups.

In analysis of the odds ratio of mortality and of developing each cardiovascular morbidity of interest annually over 7 years of follow-up within the study period, the risk of each cardiovascular morbidity associated with CKD after incident diabetes mellitus followed different trajectories. The CKD-associated risk of mortality as well as developing HF and AMI became significant soon after the diagnosis of diabetes mellitus, and remained significant throughout the study period. Conversely, the risk of PVD associated with CKD in patients with diabetes mellitus did not emerge until 4 years after diagnosis of diabetes, and the risk of IS, HS, and atrial fibrillation associated with CKD remained insignificant up to 7 years after the initial diabetes diagnosis.

The researchers cited some limitations to the study, including the retrospective analysis of prospectively collected data, using physician discretion for the diagnosis of cardiovascular morbidity, the lack of data on severity of each cardiovascular morbidity, and the inability to analyze the subgroup of patients with advanced CKD. In addition, because the cohort included only diabetic patients of Asian ethnicity, the generalizability of the findings to patients of other ethnicities is unknown.

In conclusion, the researchers said, "Using a population-based cohort of patients with newly diagnosed diabetes, we examined whether the CKD-associated risk of developing cardiovascular diseases differed depending on the disease type and the duration of diabetes mellitus. We were able to show that the risk profile could be divergent; the risk of mortality, heart failure, and AMI introduced by CKD remained significant throughout the follow-up period, while the risk of PVD did not emerge until 4 years after the initial diabetes mellitus diagnosis. On the other hand, among these newly diagnosed diabetes mellitus patients, the CKD-associated risk of IS, HS, and atrial fibrillation was insignificant. These findings are expected to shed light on the optimal strategy for detecting early cardiovascular complications among patients with incident diabetes mellitus, and facilitate the timely administration of cardiovascular care." ■

TAKEAWAY POINTS

- Researchers in Taiwan conducted a study to determine whether chronic kidney disease (CKD) in newly diagnosed diabetes mellitus differentially influences the risk of developing mortality and six prespecified cardiovascular complications.
- Patients with incident diabetes mellitus and CKD were matched with patients with incident diabetes without CKD. The risk of mortality, heart failure, and acute myocardial infarction in the group with CKD occurred soon after the diagnosis of diabetes mellitus and remained significant throughout the follow-up.
- The CKD-associated risk of peripheral vascular disease did not emerge until 4 years later; the CKD-associated risk of ischemic stroke, hemorrhagic stroke, and atrial fibrillation remained insignificant throughout the follow-up period.

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Metabolic Acidosis and Adverse Renal Outcomes

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Results were reported online in *BMC Nephrology* [doi.org/10.1186.s12882-021-02385z].

The cohort included more than 51,000 patients with CKD with or without metabolic acidosis derived from a real-world, validated, electronic medical record dataset with a follow-up period of up to 10 years. Patients in the United States with CKD and available serum bicarbonate measurements who either had at least 2 years of longitudinal follow-up or died during the 2-year period were included. Data from 2007 through 2017 were extracted from Optum's deidentified integrated electronic health record (EHR) database.

Eligible patients had at least 1 year of EHR activity with at least three eGFR results of <60 mL/min/1.73 m^2 and at least three serum bicarbonate results with at least one value between 12 and 29 mEq/L. Patients had to have two consecutive valid serum bicarbonate values 28 and 365 days apart that were either between 12 and <22 mEq/L (metabolic acidosis) or between 22 and 29 mEq/L (range of normal serum bicarbonate). Inclusion also required a baseline eGFR value between >10 and <60 mL/min/1.73 m^2.

The primary outcome of interest was the composite end point of a decline in eGFR ≥40%, renal replacement therapy (RRT), defined as chronic dialysis or kidney transplant, or all-cause mortality (DD40). Each component of the primary outcome was examined as a secondary outcome; other secondary outcomes were a kidney-specific composite outcome of RRT or a decline in eGFR ≥40% (RRT40), and RRT alone.

Of the 81 million patient records in the Optum database, 319,126 met inclusion criteria for database extraction. Of those patients, 51,558 met data sufficiency requirements, had stage 3-5 CKD with no indication of dialysis or transplant, and qualified for inclusion in the metabolic group (n=17,350) or the normal serum bicarbonate group (n=34,208).

Patients in the metabolic acidosis group had lower levels of serum bicarbonate (mean 19.7 vs 26.1 mEq/L), were younger (mean age 70.3 vs 74.3 years), were more likely to be Black (15% vs 7%), had more advanced CKD (baseline eGFR 37.2 vs 43.2 mL/min/1.73 m^2), had a greater burden of comorbidities (coronary artery disease, diabetes, hypertension, heart failure, peripheral vascular disease, and a higher comorbidity burden as measured by the Charlson Comorbidity Index [CCI]), and had higher mean urine albumin-to-creatinine ratio (ACR) (277 mg/g vs 127 mg/g), *P*<.001 for all comparisons.

At 2 years, the incidence of the composite outcome increased with CKD severity in both the metabolic acidosis group and the group with normal serum bicarbonate. Within each subgroup of CKD, the rates of the composite outcome were significantly higher among patients with metabolic acidosis compared with patients with normal serum bicarbonate: CKD stage 3a, 39% vs 12%, *P*<.001; CKD stage 3b, 43% vs 16%, *P*<.001; CKD stage 4, 59% vs 33%, *P*<.001; CKD stage 5, 87% vs 82%, *P*=.03.

The effects of selected covariates on the risk of the composite outcome were evaluated using Cox proportional hazards models over <10 years, and effects on the odds of the composite outcome were evaluated using a logistic regression model over ≤2 years.

In all models, serum bicarbonate was a significant predictor of the composite outcome. Over a 10-year period, each 1-mEq/L increase in serum bicarbonate was associated with a 7.4% decrease in the risk of the composite outcome (hazard ratio [HR], 0.926; 95% confidence interval [CI], 0.922-0.930; *P*<.001) after controlling for age, sex, race, eGFR, pre-existing diabetes, hypertension, heart failure, CCI score, and log ACR. There was also an independent association between serum bicarbonate and the 2-year composite outcome.

Over a ≤2-year period, there was an association between each 1-mEq/L increase in serum bicarbonate and a 13% decrease in the odds of the composite outcome (odds ratio [OR], 0.873; 95% CI, 0.866-0.879; *P*<.001) following adjustment for age, sex, race, eGFR, pre-existing diabetes, hypertension, heart failure, CCI score, and log ACR.

Each 1-mEq/l increase in baseline serum bicarbonate was associated with a 4.7% decrease in the risk of the kidney-specific composite outcome of RRT or a decline in eGFR ≥40% (HR, 0.953; 95% CI, 0.947-0.958; *P*<.001), a 4.5% decrease in the risk of RRT (HR, 0.955; 95% CI, 0.948-0.963), and a 9.3% decrease in the risk of all-cause mortality (HR, 0.907; 95% CI, 0.902-0.911; *P*<.001) over ≤10 years.

The significance of serum bicarbonate as a predictor of the composite outcome was sustained in subgroups analyzed by age. In the extended cohort that included patients who had missing values for urine ACR, serum bicarbonate remained a significant predictor of the composite outcome, the kidney-specific composite outcome of RRT or a decline in eGFR ≥40%, RRT, and all-cause mortality.

Limitations cited by the authors included the retrospective observational study design resulting in possible residual confounding, the lack of data from specialized providers of most dialysis care, and only considering laboratory values at baseline.

In conclusion, the researchers said, "Among patients with non-dialysis-dependent stage 3-5 CKD, low levels of serum bicarbonate within the range of metabolic acidosis are independently associated with increased risk of DD40 (reduction in eGFR >40%, RRT, or all-cause mortality), RRT40 (RRT or reduction in eGFR ≥40%), and the individual outcomes of RRT and all-cause mortality. These findings are consistent with findings from recent clinical trials. Taken together, our study, combined with evidence from randomized, controlled trials, indicate that a low serum bicarbonate level may be an important modifiable risk factor for CKD progression and mortality. Efforts to improve disease awareness and treatment of metabolic acidosis in patients with CKD are urgently needed." ■

TAKEAWAY POINTS

- Researchers conducted an observational, longitudinal, retrospective cohort study to examine the association between metabolic acidosis and progression of CKD and mortality in a large US community-based cohort.
- The primary outcome was a composite of a decline in estimated glomerular filtration rate of ≥40%, renal replacement therapy, or all-cause mortality. There was an association between low levels of serum bicarbonate within the range of metabolic acidosis and increased risk of the primary outcome.
- There was also an association between low levels of serum bicarbonate and the kidney-specific composite outcome of RRT or a decline in eGFR ≥40%.

CONFERENCE COVERAGE SPRING CLINICAL MEETINGS

Study on Anemia in CKD Treatment Preferences

One part of clinical decision making focuses on an understanding of patient and physician preferences regarding various types of treatment. There are few data available examining the value patients and physicians place on specific treatment attributes in anemia in chronic kidney disease. **Ember (Yiwei) Lu, PharmD,** and colleagues in the United States and the United Kingdom conducted a study to identify treatment attributes of value to patients and physicians and determine the relative importance of those attributes.

Results of the discrete choice experiment (DCE) study were reported during a virtual poster session at the NKF Spring Clinical Meetings 2021. The poster was titled *Patients' and Physicians' Preferences for Treatment of Anemia of Chronic Kidney Disease: Design Methods of a Discrete Choice Experiment.*

The study will include three phases. In phase one, evidence reviews and qualitative interviews were used to identify and describe relevant treatment attributes, supporting the understanding of the symptoms of anemia and their impact. In phase two, pilot interviews with patients and physicians will be used to test the design and validity of the DCE. In the third and final phase, the DCE will be conducted in the United States, Germany, and Japan in a cohort of non-dialysis-dependent and peritoneal dialysis patients, and physicians. A multinominal logit model will be used to analyze responses.

The evidence review identified potential candidate attribute categories of benefit, risk, and convenience. Benefit attributes include items such as anemia symptom relief, number of required monthly blood transfusions, social and emotional impact, need for iron supplements, and life satisfaction/quality of life. Risk attributes include serious adverse events, lung damage, risk of major cardiovascular events, and geriatric complications. Convenience attributes include mode and frequency of administration, out-of-pocket costs, and product storage. The attributes will help inform the design of semi-structured interview guides that will be used in the qualitative interviews to further refine the final attribute list that will be used in collection of the main data.

"This study will address a crucial gap in renal disease research by quantifying, comparing, and contrasting treatment attributes that patients and physicians value. Knowledge of these attributes can benefit future shared decision making in clinical practice," the researchers said.

Source: Lu E(Y), Okoro T, Amelio J, et al. Patients' and physicians' preferences for treatment of anemia in chronic kidney disease: Design methods of a discrete choice experiment. Abstract of a poster presented at the National Kidney Foundation virtual Spring Clinical Meetings 2021 (Abstract #169), April 9. 2021.

COVID-19-Related AKI In Children

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Dr. Kari et al. conducted a retrospective cohort study to examine data from all children admitted to three tertiary centers in the Kingdom of Saudi Arabia (King Abdulaziz University Hospital, King Khalid University Hospital, and East Jeddah General Hospital) with COVID-19. The researchers sought to estimate the prevalence of AKI and its associated factors, as well as the care required in that patient population. Results of the study were reported online in *BMC Nephrology* [doi.org/10.1186/s12882-021-02389-9].

All children ≤14 years of age who tested positive for COVID-19 by polymerase chain reaction of nasal swab samples and were admitted to one of the three participating centers between March 1, 2020, and July 2020 were included. Exclusion criteria were positive COVID-19 patients with insufficient data, those who were seen in the emergency department with positive swabs but did not require hospital admission, or any previous admission for COVID-19. Neonates (age <28 days) and patients with evidence of pre-existing chronic kidney disease stages 3-5 were also excluded. Clinical outcome indicators were mortality rate, abnormally high creatinine, high blood pressure, or proteinuria.

The study included 89 children admitted with a confirmed diagnosis of COVID-19. Of the 89, 21% (n=19) developed AKI following admission. Patients who developed AKI were younger than those with normal kidney function. Most of the children in both groups (AKI and non-AKI) tended to be overweight (median body mass index in the 91st percentile). Children in the AKI group had increased number of comorbidities compared with those in the non-AKI group. No patient in either group had chronic renal impairment and all had normal levels of creatinine and estimated glomerular filtration rate at baseline.

Using staging criteria from the Kidney Disease Improving Global Outcomes guidelines for AKI, 58% of patients in the AKI group had AKI stage 1, 31.5% had stage 2, and 10.5% had stage 3. In 10 of the 11 children with stage 1 AKI, renal angina index (RAI) score was <8 (insignificant). However, all children with AKI stages 2 and 3 had a significant RAI score (≥8) and all of those with AKI stage 3 had a maximum RAI score of 40.

> In patients with AKI stage 2 or 3, the NINJA indicator of significant exposure to nephrotoxic medications was more frequently positive than among patients with stage 1 AKI or those in the non-AKI group (*P*<.001).

Of the children with AKI, 15% (all with AKI stage 3) presented with the full diagnostic criteria of MIS-C, compared with only 1.5% in the non-AKI group. Renal function deteriorated earlier in those with AKI stages 2 and 3 compared with children with AKI stage 1. In patients with AKI stage 2 or 3, the NINJA (Nephrotoxic Injury Negated by Just in Time Action) indicator of significant exposure to nephrotoxic medications was more frequently positive than among patients with stage 1 AKI or those in the non-AKI group (*P*<.001). Ninety-five percent of patients with AKI were non-oliguric and no patient had any evidence of hypervolemia. RRT was not prescribed in any patient with AKI.

There was a significant association between AKI and more frequent admission to the pediatric intensive care unit (PICU) (32% vs 2.8%; *P*<.01) and mortality (42% vs 0%; *P*<.001) compared with patients in the non-AKI group. There was no significant association between AKI and prolonged hospitalization (58% vs 40%; *P*=.163) or development of MIS-C (10.5% vs 1.4%; *P*=.051), compared with patients in the non-AKI group. Following adjustment for age, sex, and the presence of comorbidities, the association between AKI and mortality remained significant (adjusted odds ratio [aOR], 14.6; *P*=.041), as did the association between AKI and admission to the PICU (aOR, 10.1; *P*=.009).

Nine percent of the study population had renal impairment at discharge, which was influenced by predictive factors including presence of comorbidities (*P*=.023), hypotension (*P*<.001), hypoxia (*P*=.02), heart failure (*P*=.001), adult respiratory distress syndrome (*P*=.005), hypernatremia (*P*=.011), abnormal liver profile (*P*=.046), high C-reactive protein (*P*=.033), and positive blood culture (*P*=.002).

The small population size of the study population was cited by the authors as a limitation to the findings, as were the retrospective design and short study duration.

In conclusion, the researchers said, "In the setting of COVID-19, AKI occurred in approximately one-fifth of our hospitalized children, and more than one-third of those required PICU admission. AKI is more commonly found in younger children and in those with comorbid conditions. AKI is associated with increased mortality and morbidity. A small proportion of children with AKI can develop residual renal impairment at the time of discharge. Nonetheless, it tends to be milder than in adults, with a lower incidence of oliguria and less need for RRT." ■

TAKEAWAY POINTS

- Researchers conducted a study to examine the prevalence of acute kidney injury (AKI) in children hospitalized with COVID-19.
- Of the 89 children in the study cohort, 21% (n=19) developed AKI (52.6% stage 1).
- There was an association between a high renal angina index score and AKI severity, and multisystem inflammatory syndrome in children was increased in those with COVID-19-related AKI compared with children with COVID-19 without AKI.

CONFERENCE COVERAGE SPRING CLINICAL MEETINGS

Outcomes in COVID-19-Related AKI Requiring RRT

Acute kidney injury (AKI) incidence among patients with COVID-19 has been reported as high as 47%, and mortality ranges from 35% to 80% in patients with COVID-19-related AKI. The risk of mortality is increased in patients with COVID-19-related AKI requiring renal replacement therapy (RRT). **Kevin Kin, DO,** and colleagues conducted a study to describe outcomes among hospitalized patients with COVID-19-related AKI requiring RRT from a large diverse population in Southern California.

Results of the retrospective cohort study were reported during a virtual poster session at NKF Spring Clinical Meetings 2021. The poster was titled *Outcomes of Hospitalized Patients with COVID-19 and Acute Kidney Injury Requiring Renal Replacement Therapy.*

The study included patients with COVID-19-related AKI requiring RRT (defined as conventional hemodialysis, continuous RRT, or both) within the Kaiser Permanente Southern California health system from March 14, 2020, through September 30, 2020. The researchers collected data on patient characteristics, comorbidities, laboratory values, modality of RRT, mortality, and RRT requirements following hospital discharge.

The cohort included 167 patients with COVID-19-related AKI requiring RRT. Median age of the cohort was 62 years. Overall, 114 (68%) patients died during the hospitalization, with a median of 8 days in RRT (range, 1-83 days). Fifty-six patients (49.1%) died within 7 days of RRT initiation, 87 (76.3%) within 14 days of RRT initiation, and 106 (93.0%) within 30 days of RRT initiation. The highest mortality rates were seen among patients with COVID-19-related AKI requiring RRT with baseline estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2 compared with 64% and 39% among patients with eGFR 30-59 mL/min/1.73 m^2 and <30 mL/min/1.73 m^2, respectively.

Among the patients who survived and no longer required RRT, mean number of RRT days was 21. Twenty-nine of the 53 patients (54.7%) who were discharged from the hospital continued to require RRT on an outpatient basis.

In conclusion, the researchers said, "Among COVID-19 patients hospitalized with AKI requiring RRT, patient survival was low (32%). For patients who survived, more than half continued to be dialysis dependent. Given our findings and as COVID treatment continues to evolve, we hope to elucidate additional factors that may impact AKI and survival in COVID-19 patients."

Source: Kin K, Gysi M, Lu D, Selevan D, Sim J. Outcomes of hospitalized patients with COVID-19 and acute kidney injury requiring renal replacement therapy. Abstract of a poster presented at the National Kidney Foundation virtual Spring Clinical Meetings 2021 (Abstract #14), April 9, 2021.

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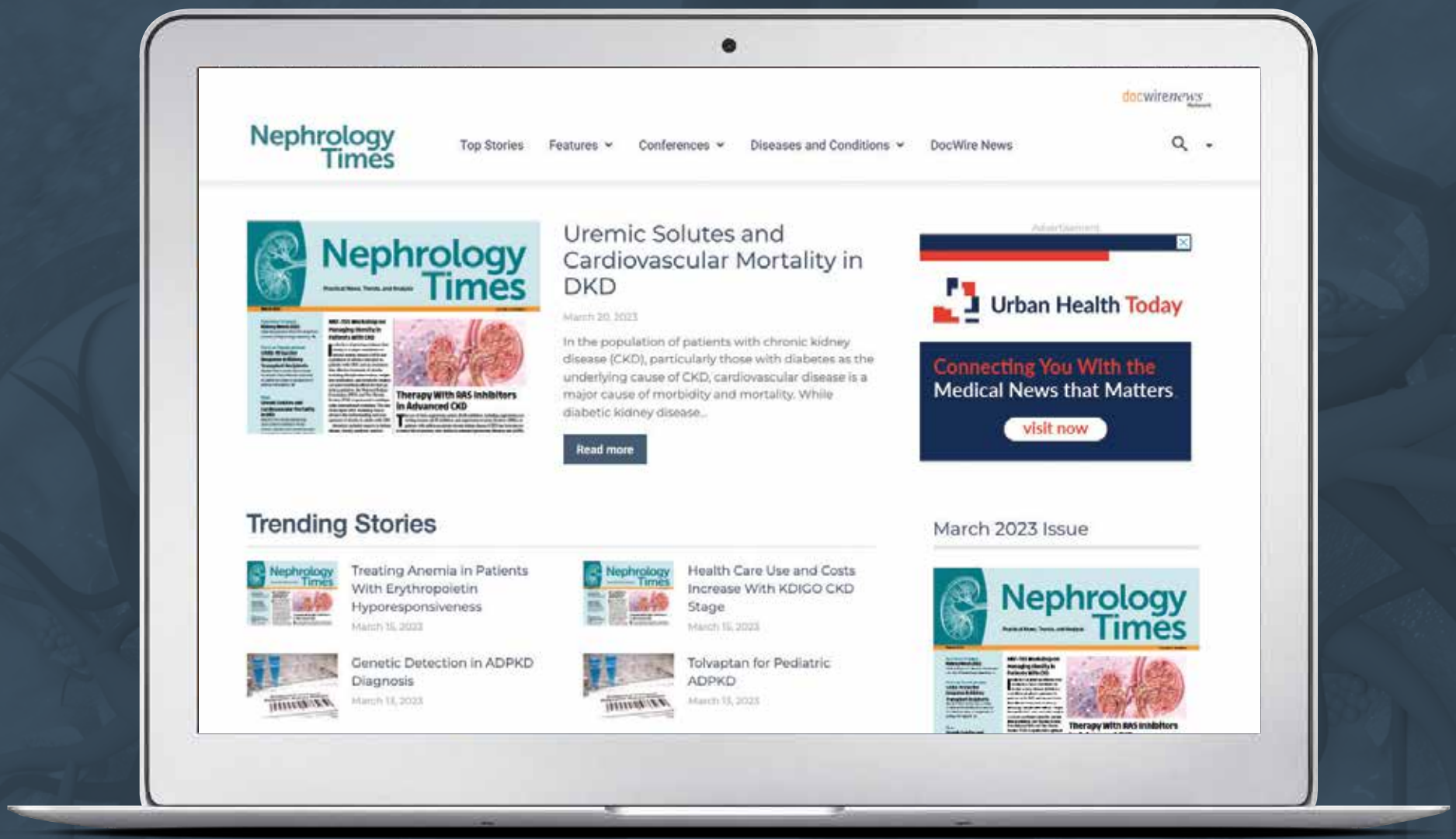

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Measures of Kidney Function as Risk Factors of Cardiovascular Outcomes in Older Adults

At present, classification of chronic kidney disease (CKD) is based on the associations of decreased estimated glomerular filtration rate (eGFR) and/or increased urinary albumin-creatinine ratio (UACR) with outcomes such as kidney failure, cardiovascular disease, and death. However, according to **Andreas Kühn, MD,** and colleagues in Germany, the strength of those associations in older patients is unclear.

The researchers conducted a population-based cohort study to examine (1) the association of kidney function with cardiovascular outcomes and mortality and (2) the predictive abilities of seven eGFR equations and UACR for those outcomes within the Berlin Initiative Study (BIS), a prospective cohort of older adults. Results were reported in the *American Journal of Kidney Diseases* [2021;77(3):386-396].

The outcomes of interest were stroke, myocardial infarction (MI), all-cause mortality, and any of the first of those events. Hazard ratios (HRs) and 95% confidence intervals (CIs) were derived from multivariable-adjusted Cox proportional hazards models for association analyses. The category-free net reclassification improvement (NRI) for all four outcomes at 5 years was used to compare discriminative abilities beween models.

The analyses were divided into two parts: (1) kidney measures as risk factors, i.e., the association of eGFR and/or UACR with cardiovascular outcomes and mortality; and (2) kidney measures as predictors, i.e., the predictive abilities of eGFR (different equations) and/or UACR for all outcomes. For part 1, GFR was estimated using the creatinine- and cystatin C-based BIS equation ($eGFR_{BIS2(cr\text{-}cys)}$), developed for individuals >70 years of age. Measured GFR (mGFR) was used for sensitivity analysis (n=436).

The BIS is a study focusing on kidney function in adults ≥70 years of age in Berlin, Germany (n=2069). The current analysis included individuals with serum creatinine, cystatin C, and UACR values available at baseline and excluded those with a previous stroke or MI by either self-report or insurance claims data. A total of 1581 participants were eligible. Of those, 904 were female and mean age was 79.7 years.

Of the 1581 eligible participants, 57.1% had eGFR <60 mL/min/1.73 m^2, UACR ≥30 mg/g was detected in 17.7% of those with eGFR 60 mL/min/1.73 m^2 and 28.9% of those with eGFR <60 mL/min/1.73 m^2.

During a median follow-up of 8.2 years, there were 193 first strokes, 125 first MIs, and 531 deaths, resulting in 683 participants with 849 events in total. Depending on the outcome, there was a median of 8.1 to 8.3 years of person-time.

For stroke, the lowest event-free survival was seen for low eGFR and any UACR (~80% after 9 years). The combination of decreased eGFR and increased UACR showed the lowest event-free survival (~85%), as well as worst overall survival, with ~70% mortality after 9 years.

When eGFR was categorized with a cut-off of 60 mL/min/1.73 m^2, the lower category was associated with HRs of 2.18 (95% CI, 1.52-3.13) for stroke, 1.15 (95% CI, 0.75-1.76) for MI, 1.26 (95% CI, 1.00-1.57) for mortality, and 1.32 (95% CI, 1.09-1.61) for any event. When eGFR was categorized as ≥60, 45 to 59, or <45 mL/min/1.73 m^2, HRs for stroke were increased in the lower two categories. For the outcomes of mortality and MI, the only statistically significant findings was the association of eGFR <45 mL/min/1.73 m^2 with mortality (HR, 1.57; 95% CI, 1.20-2.06).

There were significant associations between albuminuria with UACR of 30 to 300 mg/g and MI, (HR, 1.65; 95% CI, 1.09-2.51) and mortality (HR, 1.63; 95% CI, 1.34-1.98), and any event (HR, 1.45; 95% CI, 1.21-1.73); there was no significant association with stroke (HR, 0.91; 95% CI, 0.63-1.33). There were associations between albuminuria with UACR >300 mg/g and increased HRs for all-cause mortality and any event. The associations between albuminuria with UACR >300 mg/g and stroke and MI were less and non-significantly increased, due possibly to the limited event rate in this category.

In the 436 individuals with available mGFR, after adjusting for age and sex, the stroke risk for eGFR 45 to 59 mL/min/1.73 m^2 was independent of UACR, in contrast to the other outcomes.

In part 2 (predictive abilities of kidney measures), the predictive discrimination abilities of seven different eGFR equations, category-free NRI (asymmetric 92% CI) was estimated when adding the two dichotomized kidney measures to two different models; either eGFR and/or UACR to the basic model or eGFR to the basic UACR model. There was significant positive NRI for eGFR calculated using the cystatin C-based Chronic Kidney Disease Epidemiology Collaboration equation and the $eGFR_{BIS2(cr\text{-}cys)}$ and Full Age Spectrum equations. UACR demonstrated significant positive NRIs for MI and mortality.

Limitations to the study cited by the authors were primarily attributable to the age of the participants, multimorbidity and increased mortality may had led to bias, eGFR and UACR categorization and blood pressure measurements were based on single assessments at baseline, and the lack of data on causes of death.

In summary, the researchers said, "Our results suggest that CKD G3a with UACR <30 mg/g is strongly associated with risk for stroke but not for MI and all-cause mortality in our elderly BIS population. In contrast, UACR of 30 to 300 mg/g did not seem to be associated with stroke risk but was strongly associated with MI and all-cause mortality. This may suggest a different pathophysiologic link between CKD and stroke risk. Thus, our study supports interpreting eGFR <60 mL/min/1.73 m^2 as a risk factor for cardiovascular events in older adults, which has been an ongoing debate, even if the association was found to be weaker compared with younger persons. Furthermore, eGFR based on cystatin C level improved risk predictions of stroke in our cohort of adults older than 70 years, confirming the prognostic benefit of cystatin C level in old age." ■

TAKEAWAY POINTS

- In the general population, estimated glomerular filtration rate (eGFR) and urinary albumin-creatinine ratio (UACR) are associated with risk of cardiovascular events; the strength of that association in older adults is unclear.
- Researchers conducted a population-based cohort study to examine associations between eGFR and UACR and stroke, myocardial infarction (MI), and all-cause mortality.
- There was an association between eGFR 45 to 59 mL/min/1.73 m^2 and stroke but not MI or all-cause mortality; in contrast, UACR of 30 to 300 mg/g was associated with MI and all-cause death but not stroke.

Risk Factors for Mortality in Patients with AKI Receiving CKRT

Critically ill patients commonly develop acute kidney injury (AKI) and may require continuous kidney replacement therapy (CKRT). Developing AKI is associated with adverse patient outcomes and increases mortality rate to approximately 60% to 80%. Identification of risk factors for outcomes in patients with AKI requiring CKRT is crucial.

Results of previous studies have suggested associations between lower ratios of serum creatinine to cystatin C with both lower muscle mass and adverse clinical outcomes in multiple disease conditions. **Chan-Young Jung, MD,** and colleagues conducted a retrospective cohort study to examine the association of creatinine-cystatin C ratio in patients with AKI undergoing CKRT. Results were reported in the *American Journal of Kidney Diseases* [2021;77(4):509-516].

The primary outcome of interest was age- and sex-adjusted 90-day mortality after initiation of CKRT. Secondary outcomes included age- and sex-adjusted 30-day mortality, CKRT maintenance duration, KRT dependency at discharge, and length of intensive care unit (ICU) and hospital stays. The researchers evaluated 10 years of data in critically ill patients with AKI requiring CKRT who were treated at a single-center ICU setting. Cox proportional models were used to estimate the association between creatinine-cystatin C ratio and the study outcomes.

Patients at the 99-bed ICU of the Yonsei University Health System in Seoul, South Korea, who underwent CKRT between August 2009 and June 2019 were screened. Exclusion criteria were age <18 years and kidney failure requiring maintenance kidney replacement therapy prior to initiation of CKRT. The final analysis included 1588 patients.

Electronic medical records were used to retrieve laboratory and demographic data; baseline was defined as the time of initiation of CKRT. Decisions to initiate CKRT were made by attending nephrologists. Indications included volume overload, metabolic acidosis, hyperkalemia, and oliguria.

Mean age of the analysis cohort was 64.7 years, 40% (n=635) were female, 55.8% (n=886) had hypertension, and 37.6% (n=597) were being treated for diabetes mellitus. Median creatinine and cystatin C levels at baseline were 2.2 mg/L and 2.5 mg/L, respectively, with a creatinine-cystatin C range of 0.08 to 10.48.

Following stratification into quartiles based on baseline creatinine-cystatin C ratio, the proportion of women in each group was progressively lower across progressively greater creatinine-cystatin C ratios ($P<.001$). In groups with higher creatinine-cystatin C ratios, systolic blood pressure, diastolic blood pressure, and mean arterial pressure were significantly higher ($P<.001$). Higher creatinine-cystatin C ratios also tended to be associated with higher Acute Physiology and Chronic Health Evaluation II scores ($P<.001$). Charlson Comorbidity Index scores and 2-hour urine output prior to initiation of CKRT were comparable across quartiles.

In multivariate Cox proportional hazards regression analyses, mortality hazard ratios (HRs) for the quartiles were successively lower with greater creatinine-cystatin C ratios. For quartile 4 (highest creatinine-cystatin C ratios), HR for 30-day mortality was 0.63 (95% confidence interval [CI], 0.52-0.75); HR for 90-day mortality was 0.59 (95% CI, 0.50-0.71); both mortalities were significantly lower than in quartile 1 ($P<.001$). Following adjustment for confounding factors, the observed relationship between creatinine-cystatin C ratio and quartile mortality was maintained. There were no interactions between creatinine-cystatin C ratio and sex ($P=.3$); no sex-specific evaluations were made.

Cubic spline analyses were used to further examine the association of creatinine-cystatin C ratio with 30-day and 90-day mortality risk. There was significant decline in HRs for 30- and 90-day morality at creatinine-cystatin C ratios >0.35. The risks for 30- and 90-day mortality became progressively lower with progressively greater creatinine-cystatin C ratios. Following adjustments for confounding factors, the relationships remained.

In multivariate Cox proportional hazards regression analyses, mortality hazard ratios (HRs) for the quartiles were successively lower with greater creatinine-cystatin C ratios.

Within 30 days of CKRT initiation, 954 patients died; the number of deaths increased to 1055 (66.4%) at 90 days post-CKRT initiation. Patients received CKRT on average for 6.3 days. Mean length of stay in the ICU was 15.7 days and mean hospital length of stay was 50.3 days. At discharge, the rate of KRT dependence was 12.3%. There was a statistically significant trend toward lower 30- and 90-day mortality at higher creatinine-cystatin C ratios ($P<.001$). The length of ICU and hospital stays were significantly shorter for the higher ratio groups ($P<.001$ for both). Duration of CKRT and KRT dependence at discharge were comparable across creatinine-cystatin C ratio quartiles.

Kaplan-Meier curves revealed that cumulative 10- and 90-day survival probabilities were significantly lower for patients in the lowest baseline creatinine-cystatin C ratio quartile (quartile 1), compared with the other three quartiles ($P<.001$). Cumulative 30- and 90-day survival probability for each quartile sequentially improved with greater creatinine-cystatin C ratio.

The researchers cited some limitations to the study, including the need to use caution in interpreting the independent relationship between creatinine-cystatin C ratio and mortality due to the retrospective design of the study, the lack of data on nutritional status, and creatinine and cystatin C likely not in a steady state in the setting of AKI.

The researchers said, "In conclusion, creatinine-cystatin C ratio is associated with survival in ICU patients with AKI undergoing CKRT. This ratio may be used as a practical prognosis risk factor for ICU patients with AKI. However, further evaluations are needed for its general application." ■

TAKEAWAY POINTS

- Researchers conducted a retrospective cohort study to examine the association between creatinine-cystatin C ratio and outcomes in patients with acute kidney injury (AKI) undergoing continuous kidney replacement therapy (CKRT).
- The 30- and 90-day mortality rates were significantly lower for patients with higher creatinine-cystatin C ratios.
- Higher serum creatinine-cystatin C ratios were associated with better survival in patients with AKI in intensive care units receiving CKRT.

Updating Recommendations in Management of Dietary Phosphorous in CKD

TAKEAWAY POINTS

- Renal dietitians from the Irish Nutrition & Dietetic Institute conducted a literature review to update the phosphorous section of the Irish Renal Diet Sheet, a national reference used to educate patients with chronic kidney disease.
- The review included four priority topics: bioavailability of dietary phosphorous; safety and benefit of increasing plant protein; protein prescription; and phosphate additives.
- Three recommendations emerged: introduction of some plant protein; consideration of protein intake in terms of phosphorous load; and avoiding foods containing phosphate additives.

Hyperphosphatemia, a complication found in nearly all patients with end-stage kidney disease (ESKD), is associated with increased mortality. Even in normal ranges, elevated phosphorus levels are associated with increased mortality in earlier stages of chronic kidney disease, (CKD) as well as in some patients with normal renal function.

Restriction of dietary phosphorus is a cornerstone of dietary management of patients with CKD and hyperphosphatemia. However, according to **Fiona N. Byrne, BSc, MSC, PhD,** and colleagues, the underlying evidence for restricting dietary phosphorous in that patient population is "weak and largely justified based on clinical experience, a preponderance of observation findings, and the suspected underlying pathophysiological mechanisms."

The renal dietitians at the Irish Nutrition & Dietetic Institute opted to update the phosphorous section of the Irish Renal Diet Sheet, a national reference used in patient education efforts in Ireland; the sheet had been virtually unchanged for the past 20 years. The revised sheet calls for moderation in protein intake, restriction in dairy intake and in foods with a high total phosphorous content, and provides advice on the avoidance of phosphate additives.

A 1-day conference was held in 2015 to summarize advances and challenges in the management of dietary phosphorus of patients with CKD. The meeting included scientific and clinical experts from Ireland and the United Kingdom in addition to national stakeholders and 28 renal dieticians from renal units across Ireland. Seven of the dieticians attending agreed to conduct a review and dietary management update in two steps: (1) combine clinical experience and expertise with available research evidence; and (2) use the updated nutrient-level recommendations to develop a national modified diet sheet that could be individualized to the needs of each patient.

In a review article in the *Journal of Renal Nutrition* [2021;31(2):132-143], Dr. Byrne et al. summarized efforts to define revised dietary recommendations for phosphorus in CKD G3-5D. The group conducted a narrative review to describe the range of dietary interventions that have been examined in trials and interpret the available literature. In the literature search, they focused on nonpharmacological strategies that might improve serum phosphate control.

Identified strategies included consumption of vegetarian protein, the use of diets lower in protein, diets low in phosphorus, avoiding phosphate additives, and including egg whites and low phosphorous milks.

In some, but not all of the studies reviewed, the use of vegetarian sources including soya led to a reduction in serum phosphate. Trials of low protein intake concluded that a very low protein intake was not superior to conventional low protein intake in the effect on serum phosphate. In patients with CKD, a low phosphorus diet decreased fasting serum phosphate; although in another study, the phosphate load did not affect serum phosphate. In nondiabetic CKD patients given a high phosphorous diet, there was a significant increase in serum phosphorous. Avoidance of phosphate additives was effective in lowering serum phosphorous in a seminal study. Substituting pasteurized egg white for meat during one meal a day also appeared to be an effective diet component to lower serum phosphate.

Based on the literature review, the group agreed to include vegetarian protein, moderation of protein intake, low phosphorous intake, focus on phosphate additives, and including egg whites and milk replacers as appropriate behaviors for Irish renal patients in the revised advice.

As part of the evidence review, the researchers examined four priority topics: (1) bioavailability of dietary phosphorus; (2) the safety and benefit of increasing plant protein; (3) protein prescription and the phosphorus to protein ratio; and (4) phosphate additives. The four topics were translated into three nutrient level recommendations: (1) the introduction of some plant protein where phosphorus is largely bound by phytate; (2) consideration of protein intake in terms of phosphorus load and the phosphorus to protein ratio; and (3) an increased focus on avoiding phosphate additives.

The review resulted in three recommendations for changes in the way Irish renal dietitians manage dietary phosphorous in patients with CKD and ESKD: (1) two 7g protein exchanges of plant protein in the form of pulses and nuts, and increased intake of whole grains; (2) to ensure that patients consume sufficient protein to meet demands but not more than that, the recommendations called for more accurate prescription of protein; while the phosphorous to protein ratio was taken into consideration, it needed to be balanced against achieving variety, choice, and overall nutritional adequacy; and (3) the new recommendations called for increased focus on avoiding foods that contain phosphate additives.

In updating the national diet sheet, the dietitians combined clinical experience and expertise with available research to develop updated nutrient level recommendations. The recommendations were then used to develop a national modified diet sheet, which is individualized to the needs of each patient.

"In conclusion, our review summarized the limited evidence that supports low phosphorous dietary advice in CKD. We have also presented our interpretation of this literature in the context of our clinical experience. The lack of high-quality outcome data highlights the need for urgent research in this field, to guide clinical practice," the reviewers said. ■

Use of Inpatient Healthcare among Children and Adolescents with CKD

Chronic kidney disease (CKD) is a continuing public health problem. CKD is a progressive disease and children with CKD may progress to kidney failure requiring dialysis or kidney transplantation. Pediatric patients whose CKD does not progress to kidney failure nevertheless face multiple chronic ailments, including hypertension, cardiovascular disease, difficulties in growth, anomalies in electrolyte levels, and metabolic bone disease. Children with CKD are also at risk for acute deterioration in health secondary to infection, dehydration, and side effects associated with medications.

There are few data available on outcomes needed resources of hospitalized pediatric patients with CKD. **Zubin J. Modi, MD,** and colleagues conducted a cross-sectional national survey of inpatient healthcare use of children and adolescents with CKD. The researchers sought to generate a description of pediatric discharges associated with CKD compared with pediatric discharges associated with other chronic conditions and to improve understanding of the use of healthcare resources and outcomes of pediatric hospitalizations associated with CKD, including length of stay, cost, and mortality compared with pediatric hospitalizations associated with other chronic illnesses. Results of the study were reported in the *American Journal of Kidney Diseases* [2021;77(4):500-508].

The study utilized deidentified data from the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project Kids' Inpatients Database (HCUP-KID), a comprehensive all-payer database of inpatient discharges for children in the United States. The researchers examined HCUP-KID survey years 2006, 2009, 2012, and 2016.

During those survey years, there were an estimated cumulative 6,524,745 discharges with a chronic medical condition nationally; of those, 256,200 were discharges of patients with CKD. Mean age of the cohort with CKD was 9.9 years, 51.5% (n=131,639) were boys,, 49.1% (n=108,261) were White, 18.0% (n=39,716) were Black, 23.8% (n=52,459) were Hispanic, 3.1% (n=6817) were Asian American, 0.8% (n=1812) were Native American, and 5.1% (n=11,292) were other race/ethnicity.

Discharges associated with CKD accounted for 427,845 (95% confidence interval [CI], 391,411-464,279) hospital days per cohort year. Median length of stay in children discharged with CKD was significantly longer compared with children in non-CKD-related discharges (2.8 days vs 1.8 days). Mean length of stay was also longer in CKD-related discharges than in non-CKD-related discharges (6.7 [95% CI, 6.50-6.8] days vs 4.9 [95% CI, 4.8-5.0] days). In multivariate analyses, discharges with CKD had a 29.9% longer length of stay overall. The length of stay for both CKD and non-CKD discharges remained stable during the four cohort years.

> The proportion of in-hospital mortality in the presence of CKD was nearly double that of other chronic diseases (0.9% vs 0.5%).

Costs were higher among discharges with CKD than among discharges without CKD (median, $8755 vs $5016). Mean cost for all discharges with CKD was $1.33 (95% CI, $1.19-$1.46) billion per cohort year. Over the subsequent cohort years, costs trended up; CKD discharges increased significantly faster than other chronic disease discharges. On average, discharges with CKD had 61.3% higher costs than those without CKD. The significant interaction revealed that the magnitude of this difference increased over time, from 51.0% to 72.5% in 2016.

The presence of CKD was associated with higher risk for mortality (odds ratio, 1.51; 95% CI, 1.40-1.63). The proportion of in-hospital mortality in the presence of CKD was nearly double that of other chronic diseases (0.9% vs 0.5%).

In sensitivity analyses, discharges where CKD was a primary diagnosis had longer length of stay, higher cost, and greater mortality than both discharges with a secondary CKD diagnosis and non-CKD-related discharges. However, longer length of stay was attributable to discharges with a primary CKD diagnosis but not a secondary CKD diagnosis. Costs were higher for both primary and secondary CKD diagnoses (67.4% [95%CI, 62.8%-72.1%] and 44.6% [95% CI, 39.2%-50.3%] higher, respectively, compared with discharges with no CKD diagnosis).

A small portion of overall discharges with CKD had data available on CKD stage. The difference in length of stay between CKD and non-CKD discharges increased in a relatively stepwise manner with advancing CKD stage. Cost difference compared with discharges without CKD was lowest in CKD stage 1 (36.1% [95% CI, 11.9%-65.6%] greater) and highest in CKD stage 5 or kidney failure with replacement therapy (133.2% [95% CI, 120.2%-145.5%] greater). The odds of mortality were higher in CKD stage 3 or higher, stage not specified, and other CKD discharges, than in non-CKD discharges.

The researchers cited some limitations to the study findings, including lack of access to and adjustment for confounders including data on patient readmission and laboratory values.

In summary, the authors said, "In four cohort years between 2006 and 2016, there were 250,000 discharges in the United States due to or complicated by pediatric CKD. Pediatric hospitalizations caused or complicated by CKD were associated with longer length of stay, higher hospitalization-associated costs, and increased odds of mortality compared with hospitalizations without diagnosed CKD. These outcomes seem to be due to the higher complexity of CKD discharges compared to discharges with other chronic illnesses.

"Investigation is needed to identify modifiable patient characteristics and healthcare delivery to reduce the adverse health outcomes of pediatric CKD in the United States. It is highly likely that the costs reported represent only a small portion of pediatric CKD expenditures because much of CKD care is performed on an outpatient basis. Further investigation into direct medical and individual costs to families of children with CKD are needed to fully grasp the economic burden that pediatric CKD has on families and the healthcare system at large." ■

TAKEAWAY POINTS

- Researchers reported results of a cross-sectional national survey of hospital discharges in pediatric patients with chronic kidney disease (CKD) in comparison with children and adolescents with other chronic illnesses.
- Pediatric patients with CKD had longer length of stay, higher median costs, and increased risk of mortality compared with patients without CKD.
- In sensitivity analyses, discharges with CKD as the primary diagnosis had longer length of stay, higher costs, and increased mortality compared with discharges with secondary CKD diagnosis as well as non-CKD discharges.

ECD Kidneys Preserved with Oxygenated End-Hypothermic Machine Perfusion

The preferred standard form of treatment for end-stage kidney disease is kidney transplantation. Facing the increasing demand for kidney transplants and to shorten waiting times for patients on the transplant waitlist, the majority of transplant centers accept kidneys that have been retrieved from expanded criteria donors (ECDs), including older and higher-risk donors with multiple comorbidities.

The ECD program also results in increased rates of complications such as primary nonfunction or delayed graft function and, ultimately, reductions in long-term graft survival. Nevertheless, according to **Peri Husen, MD,** and colleagues, despite the increased risk for graft survival, the use of higher-risk kidneys is associated with significant survival benefit for recipients compared with patients remaining on maintenance dialysis.

There are two methods of preservation of donor kidneys: (1) static cold storage (SCS), where the kidney is flushed with a preservation solution at time of procurement and submerged in cold preservation solution and kept on ice until transplant; and (2) hypothermic machine perfusion (HMP) where the donor kidney is perfused with a cold machine perfusion using a device. Previous studies have suggested an association between continuous HMP of the donor kidney starting immediately after organ procurement until implantation in the recipient and reduced risk of delayed graft function and improved kidney graft survival in the first year following transplant.

A recent single-center study using SCS followed by a short-term preimplantation period of HMP (end-HMP), suggested a reduction in risk for delayed graft function in ECD kidneys. However, there are no clinical trial data providing evidence of a potential benefit. Dr. Husen et al. conducted a prospective, randomized, multicenter trial designed to compare the effect of end-HMP after SCS versus SCS alone on 1-year graft survival in ECD donor kidneys from donors who were brain dead. Results of the trial were reported online in *JAMA Surgery* [doi:10.1001/jamasurg.2021.0949].

TAKEAWAY POINTS

- Researchers explored whether short-term reconditioning of kidney grafts using oxygenated hypothermic machine perfusion after static cold storage would improve 1-year graft survival in kidneys from expanded criteria donors.
- The randomized trial results demonstrated that 1-year survival was similar between kidneys that remained on static cold storage and those that were machine perfused following static cold storage.
- There was also no difference between the two groups in secondary outcomes including delayed graft function, primary nonfunction, acute rejection, estimated glomerular filtration rate, and patient survival.

The primary end point in the intention-to-treat analysis was 1-year graft survival. Secondary end points were delayed graft function, primary nonfunction, acute rejection, estimated glomerular filtration rate (eGFR), and patient survival. Using an online randomization tool, eligible kidneys were randomly assigned to either standard SCS or the combination of SCS with subsequent oxygenated HMP (end-HMPo_2) after arrival at the recipient center.

Of the 305 randomized kidneys, 53 were subsequently excluded. The two trial arms had similar discard and withdrawal rates, resulting in 127 end-HMPo_2 and 135 SCS kidneys available for primary and secondary outcome analysis. Because machine perfusion was found to be impossible, 14 kidneys in the end-HMPo_2 group were cold stored, and six kidneys received machine perfusion for >2 hours for logistical reasons. All of the organs were included in the end-HMPo_2 arm on an intention-to-treat basis.

In both the SCS and the end-HMPo_2 arm, donor and recipient characteristics were well balanced. The calculated kidney donor risk index and the kidney donor profile index were comparable in the two treatment arms.

Median cold ischemia time, defined as the total preservation time, was 13.2 hours in the end-HMPo_2 group and 12.9 hours in the SCS group. In the end-HMPo_2 arm, median SCS time prior to placement on the perfusion device was 7.97 hours, followed by a median of 4.67 hours of hypothermic oxygenate machine perfusion.

In the end-HMPo_2 group, 92.1% (117/127) of kidney grafts were functioning at 1 year post-transplant, compared with 93.3% (126/135) in the SCS group. Both groups were similar in death-censored graft survival at 1 year post-transplant. Graft losses were due to immunological reasons (n=3), viral or bacterial infection (n=3), arterial or venous thrombosis and complications (n=5), or other reasons (n=8).

At all assessed time points, eGFR was similar in both groups and showed a steady increase over time until the 1 year timepoint. The rates of delayed graft function were numerically lower in the end-HMPo_2 group than in the SCS group (30 [23.6%] vs 38 [28.1%]); the difference did not reach statistical significance. Results of analysis of functional delayed graft function were similar, with lower rates in the end-HMPo_2 group than in the SCS group (76 [59.8%] vs 93 [68.9%]). The rates of primary nonfunction were the same in both groups.

The rates of patient death were higher in the end-HMPo_2 group than in the SCS group (9 [7.1%] vs 2 [1.5%]). Over the course of the 12 months following transplantation, the causes of death were myocardial infarction (n=5), wound infection and subsequent sepsis (n=3), multiorgan failure (n=1), unintentional cerebrovascular injury (n=1), and malignant neoplasms (n=1). With the exception of one patient, the patients in the end-HMPo_2 group who did not survive died with a functioning graft.

There were no significant differences in the two groups in rates of biopsy-proven acute rejection. Rates of patients with at least one reported adverse event were similar between the two groups, as was the incidence of at least one serious adverse event. None of the serious adverse events were attributable to the storage method.

Results of further exploratory analysis demonstrated that when stratifying for graft failure according to study group and the incidence of delayed graft function, once delayed graft function occurred, graft survival was nearly identical between kidneys that were either cold stored or machine perfused.

In citing limitations to the study, the researchers noted that the baseline assumption of 80.2% 1-year graft survival in ECD kidneys has been exceeded by far in the study's control group, and the study being statistically underpowered due to the current improved graft survival rates compared with the clinical trial data used for the statistical analysis plan.

In conclusion, the researchers said, "Reconditioning of higher-risk ECD kidneys from donors after brain death using short-term oxygenated HMP immediately prior to transplant after a period of SCS does not lead to improved graft survival or graft function when compared with simple SCS alone." ■

Tacrolimus Trough Level and Incidence of *dn*DSAs

In recent years, long-term graft survival after kidney transplantation has improved, due, in part, to advances in immunosuppressive therapy and management of complications. Transplant recipients require lifelong immunosuppressive management to prevent allograft rejection as well as nonimmunologic complications, including chronic allograft dysfunction, cardiovascular diseases, infectious diseases, malignancy, hypertension, dyslipidemia, and diabetes mellitus. There are associations between those nonimmunologic complications and long-term use of immunosuppressive medications such as steroids and tacrolimus.

Currently, tacrolimus is the primary drug used as an immunosuppressant in kidney transplant recipients. Generally, lower tacrolimus concentration is associated with both patient nonadherence and inadequate immunosuppression, leading to acute rejection via the development of *de novo* donor-specific anti-human leukocyte antigen (HLA) antibodies (*dn*DSAs), particularly during the early phase following transplantation. High tacrolimus trough levels during the maintenance period may cause progressive arteriolar hyalinosis, arteriosclerosis, and interstitial fibrosis and tubular atrophy, also leading to deterioration in graft function.

There are few data available to help inform the optimal concentration of tacrolimus for long-term use in kidney transplant recipients. **Kohei Unagami, MD,** and colleagues at the Tokyo Women's Medical University, Tokyo, Japan, conducted a retrospective study designed to examine the relationship between the maintenance of tacrolimus trough level and the appearance of dnDSAs during long-term follow-up after kidney transplantation.

The tacrolimus protocol at the Tokyo center has used a lower trough concentration since the 2000s. The review and statistical analysis evaluated the relationship between tacrolimus trough concentration and incidence of *dn*DSA over an average period of 7 years. Results were reported in *Nephrology Dialysis Transplantation* [2021;36(6):1120-1129].

Of the 994 patients who received a kidney transplant at the Department of Urology of Tokyo Women's Medical University between 2000 and 2015, the study enrolled 584. Of the 584 study participants, 164 developed *dn*DSAs during the follow-up period and 420 did not. The enrolled patients were divided into Group 1 (no *dn*DSA, n=420) and Group 2 (*dn*DSAs, n=164). Average follow-up was 7.4 years, with no significant differences between the two groups.

In Group 2, *dn*DSAs appeared on average at 812 days following kidney transplantation. There were 140 cases of Class II *dn*DSAs (85.4%) and 50 cases of Class I *dn*DSAs (30.5%). There were no differences between the two study groups with regard to sex, duration of dialysis, or renal function prior to transplant. The incidence of IGA nephropathy was significantly higher in Group 1 than in Group 2. There were no significant differences between the groups in medical history of kidney transplantation, pregnancy, or blood transfusion.

The groups were similar in donor profiles (age, sex, and blood relationship with recipients). The number of mismatches in HLA-A/B/DR was more significant in Group 2 than in Group 1 (3.4 in Group 2 vs 2.8 in Group 1; $P<.001$). Patients with preformed DSA also showed a higher incidence of *dn*DSA production (48.2% in Group 2 vs 27.1% in Group 1; $P<.001$). The two groups were similar in the immunosuppressive regimen used.

During the follow-up period, the two groups were similar in mean tacrolimus concentration. There were no significant differences in the mean tacrolimus dosage per kilogram during the follow-up period, with the exceptions of at 6 months and 1 year following transplant. For each group as a whole, the mean trough concentration of tacrolimus was within set target ranges throughout the study period. Tacrolimus trough level was monitored at every follow-up appointment at the outpatient clinic and dosage was adjusted if needed. The researchers noted that intra-patient variability in tacrolimus exposure may have occurred due to patient nonadherence, abnormal absorption following gastrointestinal tract surgery, or pharmacologic interaction with other drugs; thus, some patients showed tacrolimus trough levels outside the target ranges.

The researchers conducted a logistic regression analysis to determine expected risk factors for the development of *dn*DSAs. The average tacrolimus trough concentration of each patient during the maintenance period was calculated based on 11 time points. Risk factors were preformed DSA ($P=.001$) and HLA-A/B/DR mismatches ($P=.005$). The average tacrolimus trough concentration was not a risk factor for the development of *dn*DSAs ($P=.328$).

> In Group 2 *dn*DSAs appeared on average at 812 days following kidney transplantation. There were 140 cases of Class II dnDSAs (85.4%) and 50 cases of Class I *dn*DSAs (30.5%).

Limitations to the study included tacrolimus levels in the participants being generally within a narrow range, lack of routine measurement of plasma concentration of mycophenolic acid, and the inclusion of ABO-incompatible kidney transplant cases in the study cohort.

In conclusion, the researchers said, "Our institution has used an immunosuppression protocol with lower target tacrolimus concentrations since the 2000s, with no significant differences in *dn*DSA incidence compared with other institutions. There were no clear relationships between *dn*DSA incidence and immunosuppressive regimen or tacrolimus trough level. Most notably, there were no significant differences in tacrolimus concentration during the observation period between patients who developed *dn*DSAs and those who did not. Therefore management of kidney transplant recipients at a lower tacrolimus concentration appears not to be a main risk factor for developing *dn*DSAs and its advantages should be taken into account with regard to long-term outcomes for patients and allografts. However, as development of *dn*DSAs is closely associated with allograft deterioration, immunosuppressive therapy that prevents *dn*DSA development is still required. Thus it is important to use appropriate immunosuppressive therapies that reduce the risk of complications, including those caused by the immunological sensitization of individual recipients." ■

TAKEAWAY POINTS

- Researchers at an institution in Japan with a tacrolimus protocol that uses a lower trough concentration as immunosuppressive management in kidney transplant recipients report results of a study examining the relationship between maintenance trough levels of tacrolimus and the rate of appearance of *dn*DSAs during long-term follow-up.
- The study cohort included 584 kidney transplant recipients; of those, 164 developed *dn*DSAs during the follow-up period.
- For kidney transplant recipients whose tacrolimus trough levels were kept within a narrow range, there was no clear relationship between tacrolimus trough level and incidence of *dn*DSAs.

Conference Coverage

AMERICAN TRANSPLANT CONGRESS 2021

The American Transplant Congress is the joint annual meeting of the American Society of Transplant Surgeons and the American Society of Transplantation. The Congress provides a forum for the exchange of new scientific and clinical information related to solid organ and tissue transplantation. Presentations and posters provide information on advances in research and care to transplant physicians, scientists, nurses, organ procurement professionals, pharmacists, and other transplant professionals.

The 2021 American Transplant Congress was held virtually, providing a showcase for the latest research and advances made by the transplant community in the past year.

Simultaneous Kidney Pancreas Transplant by Insurance Status

In young, low body mass index, insulin-dependent diabetics with end-stage kidney disease (ESKD), simultaneous pancreas and kidney (SPK) transplantation offers a survival and quality of life advantage, Due to secondary complications such as retinopathy, many patients in that population are disabled and unable to meet eligibility for Medicare coverage. There is no active pancreas transplant program for patients in California with Medicaid coverage (Medi-Cal) in the greater Los Angeles metropolitan area; the nearest contracted program is in San Francisco.

Y. A. Qazi and colleagues at the Keck Medical Center at USC, Los Angeles, California, conducted a study to compare the transplant rate and waitlist mortality in diabetics less than 50 years of age based on their insurance status. Results of the study were reported in a virtual presentation at the 2021 American Transplant Congress. The presentation was titled *The Impact of Lack of Access to Simultaneous Kidney and Pancreas Transplantation Due to Insurance Ineligibility–A Single Center Analysis.*

The study included patients with insulin-dependent diabetes and ESKD who were referred to the center and were medically eligible for SPK. Inclusion criteria were age >50 years, and insurance coverage either Medi-Cal or Medicare. Data of interest were waitlist mortality, transplant rate, and type of transplant.

A total of 129 patients met eligibility criteria; of those, 47 had Medi-Cal coverage and 82 were covered by Medicare. For patients in the Medi-Cal group, waitlist mortality was 21% (10/47), no patients received a SPK transplant, and 10% (5/47) received a kidney transplant alone. For the group with Medicare coverage, waitlist mortality was 13% (11/82), and 20% (16/82) received a SPK transplant.

In conclusion, the researchers said, "In our single center analysis of young insulin-dependent diabetics with ESKD ineligible for SPK due to insurance, the waitlist mortality was almost double and transplant rate half when compared to individuals that were insurance eligible. The higher transplant rate in the Medicare group is likely the result of shorter wait times for SPK compared to kidney alone in the Los Angeles area.

"Young Medi-Cal insulin-dependent diabetes ESKD patients in the greater Los Angeles area that are unable to be listed for SPK locally due to insurance are significantly disadvantaged and suffer higher mortality and lower transplant rates. There is an urgent need for Medi-Cal to provide more local access for SPK in the greater Los Angeles area."

Source: Qazi Y.A., Villalon E, Samson D, Mon W, Smogorzewski M. The impact of lack of access to simultaneous kidney and pancreas transplantation due to insurance ineligibility–a single center analysis. Abstract of a presentation at the virtual American Transplant Congress 2021 (abstract #698), June 6, 2021.

ß2 as Marker of Kidney Function in Patients with Delayed Graft Function

Kidney transplant recipients with delayed graft function face worse short- and long-term outcomes than those without delayed graft function. According to **A. Perez-Gutierrez** and colleagues at the University of Chicago, Chicago, Illinois, there are no biomarkers to predict outcomes in patients with delayed graft function.

Serum ß2 microglobulin is a low-molecular-weight protein that strongly correlates with serum cystatin C and creatinine and is a predictor of cardiovascular events, overall mortality, and graft failure in kidney transplant recipients. There are few data on the role of the ß2 microglobulin trend in patients with delayed graft function.

During a virtual session at the 2021 American Transplant Congress, the researchers reported results of a retrospective study examining the role of the ß2 microglobulin trend in kidney transplant recipients. The presentation was titled *The Role of the ß2 Microglobulin Trend in Patients with Delayed Graft Function after Kidney Transplant*.

The study population included all kidney transplants from deceased donors performed at the center from 2014 to 2017. Exclusions were pediatric and multiple organ transplants. Inclusion criteria were measurements of serum levels of ß2 microglobulin from postoperative day 1 to day 5; ß2 microglobulin trend was defined as the difference between ß2 on postoperative day 4 and ß2 on postoperative day 1. The researchers used univariate and multivariate logistic regression.

The analysis included 150 kidney transplant recipients. Of those, 45% (n=68) had delayed graft function (median 7.5 days, range 1-51 days). Fifty percent of the patients with delayed graft function received dialysis for 1 week only. Three patients had primary nonfunction.

With the exception of the cause of kidney failure, baseline characteristics of the two groups (with and without delayed graft function) were similar. There was a strong correlation between ß2 microglobulin and delayed graft function ($P<.001$), and there was a significant correlation between ß2 microglobulin and estimated glomerular filtration rate at 1, 6, and 12 months in all patients ($P<.05$).

In the delayed graft function group, there was correlation between ß2 microglobulin trend and the duration of delayed graft function ($P=.05$). The correlation was independent of donors after circulatory death and type of kidney storage. There was no association between ß2 microglobulin and mortality or rejection.

In conclusion, the researchers said, "The ß2 microglobulin trend is a marker of kidney function useful particularly in patients with delayed graft function, because it measures the residual kidney function in the setting of dialysis. Following the trend of ß2 microglobulin in patients with delayed graft function is informative about the duration of the delayed graft function and may help make clinical decisions. Validation of this marker in a larger population of patients with delayed graft function is needed."

Source: Perez-Gutierrez A, Bachul P.J., Juengel B, et al. The role of the ß2 microglobulin trend in patients with delayed graft function after kidney transplant. Abstract of a presentation at the virtual American Transplant Congress 2021 (abstract #664), June 6, 2021.

DASH: Portal to Manage and Track Individuals Interested in PKD

The online donor screening portal DASH was established in 2016 by the National Kidney Registry (NKR) to manage and track individuals interested in paired kidney donation (PKD). The portal was designed to track individuals through all stages of evaluation, from initial interest to actual donation. Potential donors who enrolled in DASH expressed general interest in PKD or were formally seeking evaluation through an individual NKR partner center.

A.D. Waterman and colleagues conducted a study to assess progress through DASH evaluation stages and predictors of actual donation. Results of the study were reported in a virtual presentation at the 2021 American Transplant Congress titled *High Interest, Low Payoff: Understanding Opportunities for Intervention for Those Exploring but Not Pursuing Paired Kidney Donation.*

All individuals who enrolled in DASH between October 2016 and October 20, 2020, were included. Progress was tracked through four stages: (1) initial contact; (2) clinical questionnaire screening; (3) online medical history; and (4) actual donation. Failure to proceed to the next stage within a specific time frame (expired) or when clinical/psychosocial factors reported determined donor ineligibility (ruled out) resulted in removal of donors from DASH. Predictors of donation among those who completed screening were identified using multivariable logistic regression.

During the 4-year study period, a total of 111,080 contacts were received by NKR, resulting in only 1227 (1%) actual donations. Among individuals who donated, the median time from initial contact to actual donation was 206 days.

The predictors with positive associations with donation were having at least a college education (adjusted odds ratio [aOR], 1.8; 95% confidence interval [CI], 1.4-2.3), private health insurance (aOR, 2.1; 95% CI, 1.3-3.3), and being a spouse of the recipient (aOR, 1.6; 95% CI, 1.1-2.3). Predictors negatively associated with donation were being of African American race (aOR, 0.5; 95% CI, 0.4-0.8), being a friend of the recipient (aOR, 0.3; 95% CI, 0.2-0.4), leaning about PKD on social media (aOR, 0.1; 95% CI, 0.1-0.3), or having another relationship with the recipient (aOR, 0.5; 95% CI, 0.3-0.7). History of high blood pressure, high cholesterol, obesity, and current tobacco use were also negatively associated donation predictors.

In summary, the researchers said, "While over 100,000 people expressed initial interest in pursuing PKD–enough individuals to solve the entire kidney donor shortage–few actually donated a kidney. With this high level of potential interest, if we can improve education and support of individuals who begin but fail to complete PKD evaluation strategies, more PKDs might result."

Source: Waterman AD, Wood EH, Thomas A. High interest, low payoff: Understanding opportunities for intervention for those exploring but not pursuing paired kidney donation. Abstract of a presentation at the virtual American Transplant Congress 2021 (abstract #473), June 8, 2021.

Protective Effects of Converting to Belatacept Following Kidney Transplant

Calcineurin inhibitors (CNI) have adverse effects on cardiovascular risk among kidney transplant recipients. Conversion to belatacept may reduce the cardiovascular risk in that patient population. **H. Mogallapalli** conducted a study to test the hypothesis that early conversion to belatacept would result in improved patient and graft survival and lower rates of readmission within 30 days in kidney transplant recipients with congestive heart failure compared with long-term use of CNI.

Results of the study were reported during a virtual session at the 2021 American Transplant Congress. The presentation was titled *Association of Belatacept Conversion on Patient and Allograft Survival in Kidney Transplant Recipients with Congestive Heart Failure*.

The study utilized the Wisconsin Allograft Recipient Database to merge data on belatacept with the Clarity Healthline dataset that contains data on kidney transplant recipients admitted with congestive heart failure between 2014 and 2019. The *International Classification of Diseases, Tenth Revision* code I50 was used to identify patients with congestive heart failure and code E87.70 was used to identify patients with volume overload.

Study participants who switched to belatacept were categorized into early conversion (EC, defined as switched to belatacept within 1 year of transplant) and late conversion (LC, defined as switched later than 1 year after transplant). Greedy matching was used for the EC and the LC participants based on transplant date in a 1:2 allocation ratio to CNI controls (control).

The total study cohort included 301 patients. Of those, 31.5% (n=97) were in the EC group, 25.1% (n=77) were in the LC group, and 43.3% (n=133) were in the control group. Median patient survival was 2 years in the control group, 2.2 years in the EC group, and 3.4 years in the LC group ($P<.001$). There were no significant differences among the groups in the prevalence of history of myocardial infarction, congestive heart failure, and coronary artery disease at the time of transplant.

Mean time to switching to belatacept was 3.36 months in the EC group and 3.5 years in the LC group. Compared with the two belatacept groups, participants in the control group had significantly higher rate of basiliximab induction ($P=.001$), were more likely to have received a deceased donor transplant ($P=.05$), and had significantly younger donor age (43.2 years; $P=.04$).

Results of adjusted hazard models demonstrated no statistical difference in patient survival among the three groups. There was an association between belatacept and better numerical patient and graft survival (adjusted hazard ratio [aHR], 0.36; 95% confidence interval [CI], .03-3.8; $P=.4$ and aHR, 0.74; 95% CI, 0.1-7.2; $P=.8$, respectively). There was no significant difference among the groups in the rate of readmission within 30 days (18%, 11%, and 15% in controls, EC, and LC, respectively; $P=.32$).

In summary, the researchers said, "Patient and graft survival and rate of admission within 30 days post congestive heart failure hospital discharge were not significantly different among the three groups. However, the patient and graft survival rates do suggest clinically protective effects of converting patients to belatacept after transplant date."

Source: Mogallapalli H. Association of belatacept conversion in patients and allograft survival in kidney transplant recipients with congestive heart failure. Abstract of a presentation at the virtual American Transplant Congress 2021 (abstract #938), June 6, 2021.

Donor Reactive T-Cell Clones to Diagnose and Predict Rejection

In a virtual presentation at the American Transplant Congress 2021, **Y. Sambandam** and colleagues reported interim results of a single-center, nonrandomized prospective study designed to test the hypothesis that kidney transplant rejection can be diagnosed by monitoring for donor reactive T-cell (DRTC) clones in a post-transplant biopsy and noninvasively in blood and urine samples. The presentation was titled *Kidney Transplant Rejection Can Be Diagnosed or Even Predicted by Tracking Donor Reactive T-cell Clones in Post-Transplant Samples.*

From a pretransplant anti-donor mixed lymphocyte reaction (MLR) assay, CFSE-diluting CD4 and CD8 DRTCs were flow-sorted and immunoSEQ® Assay was used to identify the T-cell receptor (TcR) clonal sequences (collectively called TcR-AlloSEQ). The premise was that TcR-AlloSEQ would identify the recipient's anti-donor T-cells.

During the post-transplant period, the presence and abundance of the pre-identified DRTCs were serially monitored via immunoSEQ in kidney transplant biopsies at 3 and 12 months, and for cause, as well as in blood and urine samples at 3, 6, and 12 months and for cause.

In results of 30 of 80 standard of care kidney transplant recipients, patients were categorized as stable (n=18), rejecting (n=5), and other causes (n=7). Clones were identified as donor reactive in both CD4 and CD8 subsets from pretransplant MLR; the DTRCs were primarily from low-frequency clones in the recipient peripheral blood mononuclear cell.

DRTCs of both subsets could be detected variably in all post-transplant samples. Recipients in the stable group had low DRTCs and those in the rejecting group had significantly ($P<.002$) elevated DRTCs at months 3 and 6, and rejection in biopsy, and in blood and urine sample tests. The increase in each rejecting biopsy suggested possible use in acute rejection diagnosis. The increases in the blood and urine samples also suggested that rejection diagnosis is possible noninvasively.

The 3-month post-transplant observation of increase in DRTCs was a predictor of biopsy-proven acute rejection in three of five patients. The rejection was resolved via dosage changes of tacrolimus, mycophenolate mofetil, and prednisone along with intravenous immunoglobulin or belatacept treatment. The dosage changes also resulted in a marked decrease in the presence of DRTCs in samples at 12-months of follow-up.

In conclusion, the researchers said, "These interim results suggested that monitoring for DRTCs can diagnose an ongoing rejection and can even predict an upcoming rejection and that this can be achieved noninvasively in blood or urine. Completion of the whole study is expected to provide more insights."

Source: Sambandam Y, Kandpal M, He J, et al. Kidney transplant rejection can be diagnosed or even predicted by tracking donor reactive T cell clones in post-transplant samples. Abstract of a presentation at the virtual American Transplant Congress 2021 (abstract #224), June 7, 2021.

Outcomes in HKT after Change in Allocation System

Heart allograft allocation is the primary determinant for heart-kidney transplantation (HKT) in the United States. **S. Rao** and colleagues conducted an analysis of the Organ Procurement and Transplantation Network (OPTN) database to compare outcomes of HKT performed under the former heart allocation system (prior-HAS, October 1, 2015-October 18, 2018, n=516) and under the current HAS that prioritizes sicker patients (after October 18, 2018, n=149).

The researchers reported results of the analysis during a virtual presentation at the 2021 American Transplant Congress. The presentation was titled *Early Outcome of Heart-Kidney Transplantation in the Current Heart Allocation System in the United States.*

The analysis included de-identified data from the OPTN registry with follow-up through December 6, 2019. Data included baseline demographics, comorbidities, and the etiology of cardiac and kidney dysfunction. Inotropic and/or mechanical circulatory support were used to assess pretransplant cardiac support. Serum creatinine level at listing, the need for pretransplant dialysis, and duration of dialysis (short ≤6 weeks, medium 7-12 weeks, and long >12 weeks) were used to assess kidney dysfunction pretransplant.

The percentage of HKT among total heart transplants has increased from 5.3% in the prior-HAS era to 6.4% under the current HAS (P=.038). While the prevalence of pretransplant dialysis was similar between the two groups (~50%), a higher percentage in the current-HAS group were in the short dialysis duration group (24.5% vs 7.3%; P=.01).

Results of univariate Cox regression analysis demonstrated lower 180-day survival in the current-HAS group (87.2% vs 92.4%; hazard ratio [HR], 1.75; 95% confidence interval [CI], 1.01-3.04; P=.04) and a trend toward lower kidney allograft survival (83.9% vs 85.9%; HR, 1.60; 95% CI, 0.09-2.59; P=.05). Following adjustment for covariates, the HAS era was not an independent predictor of outcomes. Delayed graft function of kidney allograft remained a strong predictor of poorer outcomes and was higher in the current-HAS group (35% vs 26%, P=.03).

In conclusion, the researchers said, "Our study shows that the rates of HKT have continued to increase under the current HAS. Similar to the higher mortality in heart transplant recipients under the current-HAS era, patient mortality was higher in the HKT recipients too. This study highlights the need for a novel HKT allocation policy with standardized listing and allocation criteria aimed to improve HKT outcomes."

Source: Rao S, Doyle A, Brennan D, Constantinescu S. Early outcome of heart-kidney transplantation in the current heart allocation system in the United States. Abstract of a presentation at the virtual American Transplant Congress 2021 (abstract #413), June 6, 2021.

UNOS Policies 9.7 and 8.5G and Kidney Allocation in SLK Transplants

The United Network for Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) policies 9.7 and 8.5G, enacted on August 10, 2017, were issued to establish medical criteria for simultaneous liver-kidney (SLK) transplantation and create a safety net for liver transplant recipients. One policy goal was the preservation of higher quality kidneys for kidney transplant candidates considered at high risk. According to **J. Oveyssi** and colleagues in the department of internal medicine, division of transplant nephrology, UCLA, Los Angeles, California, before the adoption of these policies, nearly half of the kidney grafts transplanted for SLK purposes had a kidney donor profile index of <35%.

The researchers conducted an analysis to examine the impact of the 2017 policies on kidney grafts for liver transplant candidates. Results of the analysis were reported during a virtual session at the 2021 American Transplant Congress in a presentation titled *Status of Kidney Allocation in Liver-Kidney Transplant Before and After the UNOS/OPTN Policy.*

The researchers used the UNOS/OPTN master datafile to identify kidney transplant recipients who had previously undergone liver transplantation listed between October 1, 1987, and April 1, 2020. Groups were divided based on transplant date of January 1, 2018. Exclusion criteria included receipt of a SLK or previous kidney transplant. The analysis examined the mean and median kidney profile donor index of the kidneys transplanted and the average time to kidney transplant.

During the study period, 12,216 kidney transplants following liver transplant were performed. Of those, 2033 kidney transplants were performed after January 1, 2018. Prior to January 2018, the mean (standard deviation [SD]) and median kidney donor profile index values were 37.5% (±26.1%) and 33.0%, respectively. After January 2018, the corresponding values were 39.1% (±24.6%) and 37.0% (P=.008).

A total of 1575 age-matched kidney after liver transplants were performed before 2018 and 260 were performed after 2018. The mean (±SD) and median kidney donor index values before January 2018 were 55.0% (±25.2%) and 58.0%, respectively. The values after 2018 were 56.0% (±25%) and 59.0%, respectively (P=.6). After 2018, the average time to transplant was reduced by 27 days (P=.0001).

In conclusion, the researchers said, "The intended goals of policies 8.5G and 9.7 have been achieved, albeit modestly, since their inception. Additional follow-up is needed to ensure that these policies continue to provide a safety net for liver transplant recipients without disadvantaging at-risk kidney transplant candidates."

Source: Oveyssi J, Hussain M, Homkrailas P, Bunnapradist S. Status of kidney allocation in liver-kidney transplants before and after the UNOS/OPTN policy. Abstract of a virtual presentation at the American Transplant Congress 2021 (abstract #29), June 5, 2021.

Trends and Outcomes of Machine Perfusion in SLK

Researchers at the University of Pennsylvania, Philadelphia, Pennsylvania, conducted an analysis of data from the Scientific Registry of Transplant Recipients on simultaneous liver kidney (SLK) transplantation to determine the trends in machine pulsatile perfusion (MPP) of kidney grafts prior to SLK and the effect of MPP on graft function.

Results of the analysis were reported by **A. Chang** at the virtual 2021 American Transplant Congress. The presentation was titled *Machine Perfusion of Kidney Grafts in Simultaneous Liver Kidney Transplantation: National Trends and Outcomes.*

The retrospective cohort study included 6594 SLK recipients between 2005 and 2020 identified using the United Network for Organ Sharing database. The study compared differences in recipient and donor characteristics according to use of kidney allograft MPP. Temporal and geographic trends were examined. Predictors of MPP were evaluated using multivariable logistic regression. The relationship between MPP and delayed kidney graft function were examined using multivariable logistic regression; Cox regression was used to assess the relationship between MPP and graft survival.

A total of 1134 (17%) SLK kidney allografts were placed on MPP. Nationally, the utilization of machine perfusion in SLK increased from under 3% in 2005 to 25% in 2020. However, there is significant variability among centers.

Allografts that underwent MPP were older (median 36 vs 34 years of age, P<.001), had a higher percentage of donor diabetes (6.3% vs 4.2%, P<.01), came from deceased donors (7.9% vs 4.5%, P<.01), and had longer cold ischemic time (12.9 hours vs 9.9 hours, P<.01). The primary determinant of MPP use was center preference (intraclass correlation 64%; only 36% of variability in MPP use was explained by donor or recipient factors).

In multivariable analysis, there was a possible trend toward reduced delayed graft function with MPP (odds ratio, 0.81; P=.08). There was no significant difference in adjusted graft survival (hazard ratio, 0.95; P=.54).

In summary, the researchers said, "Despite increasingly widespread use of MPP for storage of kidney allografts prior to transplantation, this technique does not appear to alter outcomes in simultaneous liver and kidney transplantation."

Source: Chang A, Chen M, Abt P, Bittermann T. Machine perfusion of kidney grafts in simultaneous liver kidney transplantation: National trends and outcomes. Abstract of a presentation at the virtual American Transplant Congress 2021 (abstract #138), June 6, 2021.

Outcomes in Simultaneous Heart and Kidney Transplants

Patients with advanced heart failure commonly develop kidney dysfunction. Treatment for patients with end-stage heart failure and severe kidney dysfunction with simultaneous kidney and heart transplants (SKHT) is gaining acceptance. From 2000 to 2019, there was a rise of 650% in SKHT in the United States. However, according to **K. A. Agarwal** and colleagues, despite the increasing numbers of SKHT, the selection criteria are not well defined and vary across transplant centers.

The researchers conducted a retrospective cohort study designed to identify heart transplant candidates who may benefit from a SKHT. Results of the study were reported during a virtual presentation at the 2021 American Transplant Congress. The presentation was titled *Cardiac Outcomes in Isolated Heart and Simultaneous Kidney and Heart Transplants in the US*.

The United Network for Organ Sharing database was used to compare patient and cardiac allograft survival for SKHT recipients with heart transplant alone (HTA) recipients between 1987 and 2019. The researchers also performed a subgroup analysis in recipients with post-transplant acute kidney injury (AKI) requiring renal replacement therapy (RRT) to compare outcomes between SKHT and HTA recipients.

The final analysis included 61,410 HTA and 1507 SKHT recipients. Patient survival was comparable between SKHT and HTA groups (12.4 years vs 11.3 years). However, there was a significant survival benefit from SKHT in patients who were dialysis dependent pretransplant (12.4 years vs 9.9 years). Cardiac graft survival was better in SKHT (12.5 years vs 11.2 years).

Significant risk factors for AKI requiring dialysis post-transplant were age <30 years (odds ratio [OR], 1.27), higher body mass index (OR, 1.02), reduced glomerular filtration rate (GFR) (OR, 9.46 for GFR <30 mL/min/1.73 m^2; OR, 2.68 for GFR 30 to 44 mL/min/1.73 m^2; and OR, 1.99 for GFR 45 to 59 mL/min/1.73 m^2), mechanical cardiac support (OR, 1.28), recipient diabetes (OR, 1.15), inotropic support (OR, 1.11), and prior sternotomy (OR, 1.61). Among patients with AKI requiring RRT, survival was significantly better among SKHT recipients compared with HTA recipients (11.9 vs 2.7 years).

"Our data support consideration of SKHT in dialysis-dependent heart transplant candidates and suggest that patients who are at increased risk of requiring RRT post-heart transplant may also benefit from SKHT," the researchers said.

Source: Agarwal, K.A., Patel H, Agrawal N, Cardarelli F, Goyal N. Cardiac outcomes in isolated heart and simultaneous kidney and heart transplants in the US. Abstract of a presentation at the virtual American Transplant Congress 2021 (abstract #624), June 6, 2021.

> Patients who are at increased risk of needing RRT post-transplant surgery may benefit from simultaneous kidney-heart transplant.

Outcomes of Simultaneous Kidney Pancreas Transplant versus Kidney Transplant Alone

X. Y. Fu and colleagues at Tianjin First Central Hospital, Tianjin, China, performed a retrospective analysis to compare renal function, metabolic profiles, and survival outcomes of patients undergoing simultaneous pancreas kidney transplantation (SPK) and those of patients undergoing kidney transplantation alone (TKA) among patients with end-stage kidney disease and type 2 diabetes mellitus. Results of the analysis were reported during a virtual session at the 2021 American Transplant Congress in a presentation titled *Superior Metabolic Function of Type 2 Diabetes Mellitus Patients after Simultaneous Kidney Pancreas Transplantation Compared with Kidney Transplantation Alone*.

The cohort included patients with ESKD and diabetes at the hospital who underwent SPK (n=85) or KTA (n=71). The analysis examined general demographic data, perioperative parameters, postoperative blood glucose and lipid profiles, complications, and survival outcomes in the two cohorts. Mixed effect model was used to compare repeated data.

In general, recipients of SPK were younger than recipients of KTA (49.01 vs 52.14 years; P=.018) and the age of donors was younger in the SPK group than in the KTA group (32.1 vs 47.14 years; P<.001). Renal function and metabolic outcomes were superior in the SPK group in estimated glomerular filtration rate level, lower fasting serum glucose level, lower triglyceride level, and lower cholesterol level. The rate of infection was higher in the KTA alone group (38% vs 22.4%; P=.003). Survival outcomes were similar between the two groups.

In summary, the researchers said, "SPK provides better renal function and metabolic outcomes, but has higher rate of infection than KTA for ESKD-diabetes patients. The 5-year survival outcomes of recipients and grafts were comparable between the two groups."

Source: Fu X.Y., Yu C, Wang H, et al. Superior metabolic function of type 2 diabetes mellitus patients after simultaneous kidney/pancreas transplantation compared with kidney transplantation alone. Abstract of a presentation at the virtual American Transplant Congress 2021 (abstract #896), June 6, 2021.

Early Education and Preparation for Transplant in Patients with CKD

There is consensus regarding the need to educate patients with chronic kidney disease (CKD) about transplant; however, there are often delays in initiation of transplant education, resulting in limited time for patients to make optimal decisions regarding renal replacement therapy (RRT). **R. Pines** and colleagues conducted a study to examine levels of transplant-related knowledge and actions among kidney patients in various stages of CKD and by primary language spoken.

The researchers reported results of the study during a virtual presentation at the 2021 American Transplant Congress. The presentation was titled *Understanding Early Transplant Preparation: CKD 3-5 Patients' Transplant Knowledge and Actions at Kaiser Permanente Southern California*.

The study cohort included 971 patients at Kaiser Permanente Southern California. Of the 971 patients, 41.2% had CKD stage 3, 34.4% had CKD stage 4, and 24.4% had CKD stage 5. Twenty-eight percent were Spanish-speaking Hispanic, 22% were White, 22% were English-speaking Hispanic, 18% were Black, and 10% were Asian.

The patients were surveyed about their knowledge of CKD symptoms in a 6-item questionnaire (e.g., increased fatigue is a CKD symptom) and transplant in a 20-item questionnaire (e.g., patients can live longer with a transplant than on dialysis). Twenty-five possible RRT actions were divided into three groups: (1) learning actions; (2) making informed decisions about RRT; and (3) pursuing transplant. Patients were asked whether they had already taken any of the actions.

Overall, the patients answered correctly to 58% of the items on CKD symptoms and 20% of the items on transplant knowledge. Most had taken only few steps to learn more (median: 0 of 5 steps), make informed decisions about RRT options (median: 2 of 6 steps), and pursue transplant (median: 0 of 6 seps). Patients in earlier CKD stages and those who spoke Spanish had poorer knowledge of CKD symptoms and transplant and took fewer action steps overall.

In conclusion, the researchers said, "Patients in earlier CKD stages and Spanish-speakers are less knowledgeable and less likely to take transplant-related actions, however, all patients need greater support with RRT decision-making and pursuit of transplant. Educational interventions that engage patients earlier in their CKD progression may increase informed decision-making and pursuit of living-donor kidney transplant."

Source: Pines R, Kawakita S.H., Kim G.H., et al. Understanding early transplant preparation: CKD 3-5 patients' transplant knowledge and actions at Kaiser Permanente Southern California. Abstract of a presentation at the virtual American Transplant Congress 2021 (abstract #881), June 6, 2021.

Delayed Graft Function Days and Graft Outcomes

There is some controversy related to the association of delayed graft function and the risk of acute rejection and graft survival. According to **P. Budhiraja** and colleagues at the Mayo Clinic Arizona, Phoenix, Arizona, this may be due to delayed graft function being reported as a dichotomous outcome that does not account for the difference in days of delayed graft function.

During a virtual presentation at the 2021 American Transplant Congress, the researchers reported results of a study designed to identify predictors and impact of delayed graft function on graft outcomes. The presentation was titled *Days of Delayed Graft Function and Its Impact on Graft Outcomes in Deceased Donor Kidney Transplant*.

The study cohort included patients who received deceased-donor kidney transplant at the center from 2003 to 2019. Due to acceptance of kidneys with high kidney donor profile index, long cold ischemia time (CIT), and donor kidneys with acute kidney injury, the rates of delayed graft function at the center are high. Cases with primary nonfunction unrelated to delayed graft function and pre-emptive transplants were excluded.

The Kruskal-Wallis test was used to compare recipient and donor characteristics by delayed graft function status. The analysis examined risk factors for delayed graft function status and increased delayed graft function days. Chronic changes on the protocol biopsy performed from pretransplant to months 4 and 12 were compared. Unadjusted and adjusted Cox Proportional hazard model was used to assess graft survival, censoring for death events.

The total cohort included 701 recipients without delayed graft function and 1021 recipients with delayed graft function. In multivariable analysis, there were significant associations between higher delayed graft function days and dialysis vintage, donation after cardiac death status, CIT, donor age, and donor oliguria. Acute rejection was associated with the presence of delayed graft function; there was no association between acute rejection and delayed graft function days.

In the multivariable Cox proportional hazard model, the risk for BK-virus infection and graft survival was not associated with delayed graft function days. At the 12-month biopsy, each additional day of delayed graft function conferred 4.5% increased odds of chronic interstitial fibrosis progression and 3.7% increased odds of chronic tubular atrophy progression from baseline.

"This is the first large cohort study to report the impact of delayed graft function days on progression of fibrosis, rejection, and graft survival. There is no higher risk of rejection, infection, or graft survival. However, we did find association of delayed graft function days with progression of fibrosis," the researchers said.

Source: Budhiraja P, Butterfield R.J., Misra S.S., et al. Days of delayed graft function and its impact on graft outcomes in deceased donor kidney transplant. Abstract of a presentation at the virtual American Transplant Congress 2021 (abstract #837), June 6, 2021.

Outcomes among Kidney Transplant Recipients with COVID-19

Researchers, led by S. Ismail, conducted a systematic review of published literature on clinical outcomes and management of adult kidney transplant recipients with COVID-19 with an eye toward synthesis of the evidence available on therapeutic interventions and clinical outcomes in that patient population. Results of the review were reported during a virtual session at the 2021 American Transplant Congress in a presentation titled *Clinical Outcomes and Management of COVID-19 Patients among Kidney Transplant Recipients: A Systematic Review*.

The literature search included PubMed, EMBASE, and the Cochrane registry for systematic reviews, as well as clinicaltrials.gov. There was no language restriction and articles of interest were published from November 1, 2019, to August 13, 2020. Studies of other organ transplants or dual organ transplants were excluded. The primary outcome of interest was the use of therapeutics for the treatment of COVID-19, alterations of immunosuppressive regimens, and clinical progression among kidney transplant recipients with COVID-19.

The search identified 90 eligible studies representing 1052 kidney transplant recipients. Of those, 68 were case reports or case series, representing 155 kidney transplant recipients. Among the 155 patients, 44 received intravenous steroids and 55% continued their oral maintenance steroid doses. Aminoquinolines, azithromycin, antivirals, and tocilizumab were used for 100, 64, 38, and 24 kidney transplant recipients, respectively. Acute kidney injury (AKI) occurred in 56.5%; 15 required renal replacement therapy (RRT). Twenty-five patients were admitted to the intensive care unit (ICU); median length of stay in the ICU was 10 days. Median length of hospital stay was 17 days. Death occurred in 22.6% of patients. Antimetabolites were withheld or doses reduced in 90.9% of patients.

The search also identified 23 aggregate-level studies, representing 897 kidney transplant recipients. Among those patients, 26.5% died and 35.11% developed AKI, 37 of whom required RRT. Hydroxychloroquine, azithromycin, and tocilizumab were used for 813, 491, and 373 kidney transplant recipients, respectively. Antimetabolites were stopped in 51.2%, calcineurin inhibitors were stopped or doses reduced in 320 patients, and steroid dose was increased in 222 patients.

"Kidney transplant recipients diagnosed with COVID-19 present a vulnerable population with high risk of severe clinical outcomes, including AKI, ICU admission, and mortality. A careful risk-benefit assessment between the use of antiviral drugs and the interruption of maintenance immunosuppressive agents including steroids is likely to be an important factor in the treatment of COVID-19 in this group," the researchers said.

Source: Ismail S, Banonj A, Harbi S Al, Babonj A, Almalki A, Murray E.J. Clinical outcomes and management of COVID-19 patients among kidney transplant recipients: A systematic review. Abstract of a presentation at the virtual American Transplant Congress 2021 (abstract #787), June 6, 2021.

VADADUSTAT FOR ANEMIA IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Anemia is a common complication of chronic kidney disease (CKD) and is associated with a reduced health-related quality of life, an increase in the need for red blood cell transfusions, and an increased risk for cardiovascular events. Standard care for the management of anemia in patients with CKD is the use of erythropoiesis-stimulating agents (ESAs) (recombinant human erythropoietin and its derivatives). Previous studies have demonstrated an increase in the risk of stroke, vascular access thrombosis, and death associated with the use of ESAs to target hemoglobin concentrations in the normal or near-normal range in patients with CKD, resulting in recommendations for caution in the use of ESAs and for only partial correction of anemia in that patient population.

Hypoxia-inducing factor (HIF) stimulates erythropoietin production by the liver and kidneys. HIF is regulated by oxygen-dependent proteasomal degradation through a family of prolyl hydroxylases that serve as oxygen sensors. HIF prolyl hydroxylase inhibitors represent a recently developed class of compounds that stabilize HIF, thereby stimulating endogenous erythropoietin production and ultimately erythropoiesis.

Vadadustat is an investigational oral HIF prolyl hydroxylase inhibitor in development for the treatment of CKD-related anemia. The phase 3 development process included four phase 3 trials: two that included patients with non-dialysis-dependent CKD (PRO_2TECT) and two that included patients with dialysis-dependent CKD (DD-CKD) ($INNO_2VATE$). All four trials evaluated the cardiovascular safety and efficacy of vadadustat compared with darbepoetin alfa.

$INNO_2VATE$ Trials

Kai-Uwe Eckardt, MD, and colleagues reported results of the $INNO_2VATE$ trials evaluating the cardiovascular safety and hematologic efficacy of vadadustat compared with darbepoetin alfa [*New England Journal of Medicine*; 2021;384(17):1601-1612].

The primary safety end point of interest (assessed in a time-to-event analysis) was the first occurrence of a major cardiovascular event (MACE, a composite of death from any cause, a nonfatal myocardial infarction [MI], or a non-fatal stroke), pooled across the trials (noninferiority margin, 1.25). A secondary safety point was the first occurrence of a MACE plus hospitalization for either heart failure or a thromboembolic event. The primary efficacy end point was the mean change in hemoglobin from baseline to weeks 24 and 36; the key secondary efficacy end point was the change in hemoglobin from baseline to weeks 40 to 52, in each trial (noninferiority margin, –0.75 g per deciliter).

The starting dose of vadadustat was 300 mg orally once daily, with doses of 150, 450, and 600 mg available for dose adjustment to a maximum of 600 mg per day. Darbepoetin alfa was administered subcutaneously or intravenously; the initial dose was based on the previous dose, or, in the case of patients who had not received darbepoetin alfa prior to randomization, on information on the product label.

A total of 3923 patients underwent randomization across the two trials: 369 in the incident DD-CKD trial and 3354 in the prevalent DD-CKD trial. Median duration of follow-up was 1.2 years in the incident DD-CKD trial and 1.7 years in the prevalent DD-CKD trial.

In both trials, baseline characteristics of the two treatment groups were generally well balanced with the exception that in the incident DD-CKD trial the percentage of patients with diabetes mellitus was higher among patients randomized to the vadadustat group than among those randomized to the darbepoetin alfa group (58.0% vs 51.1%).

The safety end points analyses were based on the pooled safety population: 1947 in the vadadustat group and 1955 in the darbepoetin alfa group. A first MACE occurred in 18.2% of patients in the vadadustat group (355/1947) and in 19.3% of patients in the darbepoetin alfa group (377/1955) (hazard ratio [HR], 0.96; 95% confidence interval [CI], 0.83-1.11). In the vadadustat group, the percentages and numbers of patients in whom the first MACE was death from any cause, a nonfatal MI, or a nonfatal stroke were 13.0% (253), 3.9% (76), and 1.3% (26), respectively. The corresponding percentages and numbers in the darbepoetin alfa group were 12.9% (253), 4.5% (87), and 1.9% (37), respectively.

Within each trial, the results were qualitatively consistent; however, the CI in the incident DD-CKD trial was wide (incident DD-CKD trial: HR of a first MACE, 0.97; 95% CI, 0.54-1.76; prevalent DD-CKD trial: HR, 0.96; 95% CI, 0.83-1.12).

In the incident DD-CKD trial, the mean differences between the groups in the change in hemoglobin concentration were –0.31 g per deciliter (95% CI, –0.53 to –0.10) at weeks 24 to 36, and –0.07 g per deciliter (95% CI, –0.34 to 0.19) at weeks 40 to 52. In the prevalent DD-CKD trial, the mean differences were –0.17 g per deciliter

(95% CI, –0.23 to –0.10) at weeks 24 to 36, and –0.18 g per deciliter (95% CI, –0.25 to –0.12) at weeks 40 to 52.

In the incident DD-CKD trial, the incidence of at least one adverse event was 83.8% of patients in the vadadustat group and 85.5% of patients in the darbepoetin alfa group. The incidence of any serious adverse event was 49.7% in the vadadustat group and 56.5% in the darbepoetin alfa group.

In the prevalent DD-CKD trial, the incidence of at least one adverse event was 88.3% in the vadadustat group and 89.3% in the darbepoetin alfa group. The incidence of any serious event was 55.0% in the vadadustat group and 58.3% in the darbepoetin alfa group.

In the prevalent DD-CKD trial, 88.3% of patients in the vadadustat group had at least one adverse event; 89.3% of patients in the darbepoetin alfa group had at least one adverse event. Serious adverse events occurred in 55.0% of the vadadustat group and 58.3% of the darbepoetin alfa group.

Common adverse events across all four trials included hypertension, diarrhea, pneumonia, hyperkalemia, fluid overload, fall, headache, hypotension, nausea, urinary tract infection, and cough.

The authors cited some limitations to the two trials: the investigators were aware of the treatment assignments, precluding a meaningful evaluation of patient-reported physical function and fatigue; lack of measurement of residual kidney function; the use of darbepoetin alfa as control in both trials; and lack of real-world data from longer-term clinical practice.

In summary, the researchers said, "In these two trials, we found that vadadustat was noninferior to darbepoetin alfa with respect to cardiovascular safety and correction and maintenance of hemoglobin concentrations in patients with CKD who were undergoing dialysis."

The trials were supported by Akebia Therapeutics and Otsuka Pharmaceutical.

TAKEAWAY POINTS

- Results of the INNO$_2$VATE trials examining the safety and efficacy of vadadustat as compared with darbepoetin alfa for anemia in patients undergoing dialysis were reported.
- The primary safety end point was the first occurrence of a major adverse cardiovascular event in patients with anemia and incident or prevalent dialysis-dependent chronic kidney disease; the primary efficacy end point was change in hemoglobin from baseline to weeks 24 to 36.
- Compared with darbepoetin alfa, vadadustat was noninferior in cardiovascular safety and correction and maintenance of hemoglobin concentrations among patients with anemia and CKD undergoing dialysis.

PRO$_2$TECT Trials

Glenn M. Chertow, MD, MPH, and colleagues reported the results of the PRO$_2$TECT trials among patients with anemia and non-dialysis-dependent chronic kidney disease (NDD-CKD) [*New England Journal of Medicine*; 384(17):1589-1600]. The study population included patients with NDD-CKD not previously treated with an erythropoiesis-stimulating agent (ESA) and a hemoglobin concentration of <10 g per deciliter and patients with ESA-treated NDD-CKD and a hemoglobin concentration of 8 to 11 g per deciliter (in the United States) or 9 to 12 g per deciliter in other countries.

The primary safety end point of interest (assessed in a time-to-event analysis) was the first occurrence of a major cardiovascular event (MACE, a composite of death from any cause, a nonfatal myocardial infarction [MI], or a non-fatal stroke), pooled across the trials (noninferiority margin, 1.25). A secondary safety point was the first occurrence of expanded MACE (MACE plus hospitalization for either heart failure or a thromboembolic event). The primary efficacy end point was the mean change in hemoglobin from baseline to weeks 24 and 36; the key secondary efficacy end point was the change in hemoglobin from baseline to weeks 40 to 52, in each trial.

The starting dose of vadadustat was 300 mg orally once daily, with doses of 150, 450, and 600 mg available for dose adjustment to a maximum of 600 mg per day. Darbepoetin alfa was administered subcutaneously or intravenously; the initial dose was based on the previous dose, or, in the case of patients who had not received darbepoetin alfa prior to randomization, on information on the product label.

A total of 3476 patients underwent randomization; 1751 patients were randomized to the trial among ESA-untreated patients (879 in the vadadustat group and 872 in the darbepoetin alfa group) and 1725 (862 in the vadadustat group and 863 in the darbepoetin alfa group) were randomized to the trial involving patients previously treated with an ESA. Median duration of follow-up was 1.63 years in the ESA-untreated trial and 1.80 years in the previously ESA-treated trial. The randomized groups were generally well balanced in both trials.

The safety analyses were conducted using all patients who received at least one dose of the trial drug (safety population) pooled across the two trials: 1739 in the vadadustat group and 1732 in the darbepoetin alfa group. A first MACE occurred in 22.0% of patients (382/1739) in the vadadustat group and 19.9% of patients (344/1732) in the darbepoetin alfa group (hazard ratio [HR], 1.17; 95% confidence interval [CI], 1.01-1.36). The HR did not meet the prespecified noninferiority margin of 1.25.

In subgroup analyses of MACE, death from any cause occurred in 18.3% of patients (n=319) in the vadadustat group and 17.7% of patients (n=307) in the darbepoetin alfa group; nonfatal MI in 3.9% (n=67) and 2.8% (n=48), respectively; and nonfatal stroke in 2.0% (n=34) and 1.6% (n=28), respectively. The first expanded MACE occurred in 25.9% of patients (n=451) in the vadadustat group and 24.5% of patients (n=424) in the darbepoetin alfa group (HR, 1.11; 95% CI, 0.97-1.27).

The time to CKD progression was similar between the two treatment groups in the two trials. Mean systolic and diastolic blood pressures in the two treatment groups were similar over the course of both trials.

The mean differences between groups in the change in hemoglobin concentration at weeks 24 through 36 were 0.05 g per deciliter (95% CI, –0.04 to 0.15) in the trial with ESA-untreated patients and –0.01 g per deciliter (95% CI, –0.09 to 0.07) in the trial among ESA-treated patients, meeting the prespecified noninferiority margin of –0.75 g per deciliter.

In the ESA-untreated NDD-CKD trials, the incidence of at least one adverse event was 90.9% in the vadadustat group and 91.6% in the darbepoetin alfa group. The incidence of any serious adverse event was 65.3% in the vadadustat group and 64.5% in the darbepoetin alfa group.

In the ESA-treated NDD-CKD trials, the incidence of at least one adverse event was 89.1% in the vadadustat group and 87.7% in the darbepoetin alfa group. The incidence of any serious adverse event was 58.5% in the vadadustat group and 56.6% in the darbepoetin group.

Common adverse events across all trials were diarrhea, end-stage renal disease hyperkalemia, hypertension, peripheral edema, fall, pneumonia, urinary tract infection, and nausea.

The primary study limitation cited by the authors was, based on guidance from regulatory agencies, the trials were not placebo-controlled.

In summary, the researchers said, "In these two trials, we found that, among patients with NDD-CKD, vadadustat was noninferior to darbepoetin alfa with regard to hematologic efficacy but did not meet the prespecified noninferiority criterion for cardiovascular safety, which was a composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke."

The trials were supported by Akebia Therapeutics and Otsuka Pharmaceutical.

TAKEAWAY POINTS

- Results of the PRO$_2$TECT trials examining the safety and efficacy of vadadustat as compared with darbepoetin alfa for anemia in patients with non-dialysis-dependent chronic kidney disease (NDD-CKD) were reported.
- The primary safety end point was the first occurrence of a major adverse cardiovascular event in patients with CKD-related anemia who had not received previous treatment with an erythropoiesis-stimulating agent (ESA) and in patients with anemia actively treated with ESAs; the primary efficacy end point was change in hemoglobin from baseline to weeks 24 to 36.
- Vadadustat met the prespecified noninferiority criterion for hematologic efficacy but did not meet the prespecified noninferiority criterion for cardiovascular safety.

Voices for Kidney Health

The National Kidney Foundation (NKF) has launched Voices for Kidney Health™, a community of kidney patient and health professional advocates who work with elected officials and other public leaders to create policies and initiatives to promote kidney health and ways to support patients living with kidney disease.

In a recent press release, **Kevin Longino,** CEO of the NKF and a kidney transplant recipient, said, "Voices for Kidney Health advocates work tirelessly to advance pro-kidney health policies that will help prevent or delay kidney disease. We are deeply grateful for the many voices united across the country in their efforts to push for legislative and policy victories like the national immunosuppressive Drug Coverage legislation that passed last December, as well as state bills passed to protect living organ donors. These individual stories make up a collective voice that strengthens our ability to secure additional victories for the 37 million adults in the US affected by kidney disease."

Advocates and the elected officials who represent them understand the importance of dealing with the outsized impact kidney disease has on communities of color. The community will work to collectively address disparities in kidney disease and kidney care as a key part of the advocacy agenda.

FDA Accepts NDA Filling for Vadadustat

In a joint press release, Akebia Therapeutics, Inc. and Otsuka Pharmaceutical Co., Ltd. Announced that the US FDA accepted for filing the New Drug Application (NDA) for vadadustat for the treatment of anemia due to chronic kidney disease (CKD) in patients with non-dialysis dependent CKD as well as those on dialysis. The FDA has assigned the application standard review and a Prescription Drug User Fee Act target action date of March 29, 2022. The agency is not planning on holding an Advisory Committee meeting to discuss the application.

John P. Butler, CEO of Akebia, said, "The acceptance of our vadadustat NDA filing marks another important milestone for Akebia and Otsuka, as we work to bring a new oral treatment option for patients living with anemia due to CKD. We remain confident in the clarity and quality of our data, and we look forward to working with the FDA during their review of our application. In addition, we continue to collaborate with our partners to ensure we are well positioned to support a successful commercial launch of vadadustat, upon FDA approval."

Otsuka board member and president and CEO of Otsuka's North American pharmaceutical business, **Kabir Nath,** said, "With Akebia, we are proud to have achieved this milestone in the development of vadadustat. This achievement highlights the team's ongoing execution as well as our shared commitment to advancing vadadustat with the goal of bringing this novel therapeutic to patients as soon as possible, subject to regulatory approval."

Akebia and Otsuka are collaborating on the development and commercialism of vadadustat in the United States, Europe, China, Russia, Canada, Australia, the Middle East, and other territories. They are working to prepare a Marketing Authorization Application for vadadustat for submission to the European Medicines Agency later this year.

Texas Enacts Living Donor Protection Law

In late Spring, Texas governor Greg Abbott signed H.B. 317 into law. The law provides protections for living organ donors, including prohibiting life, disability, and long-term insurers from discriminating against living organ donors by declining or limiting coverage due to their status as an organ donor, charging more for a policy, and from precluding a person from donating all or part of an organ as a condition of their policy.

The American Kidney Fund (AKF) worked with sponsors of the bipartisan bill, including Rep. Andrew Murr in the House and Sen. Boris L. Miles, a kidney transplant recipient, in the Senate to move the bill through the Texas legislature. AKF is conducting a nationwide effort to pass living donor protections at the state level. Since 2019, 16 states have signed the bills into law, including New Jersey, Washington, Pennsylvania, and Kentucky.

In a recent press release, **LaVarne A. Burton,** president and CEO of AKF, said, "The American Kidney Fund applauds Texas for enacting legislation that will ensure no one who chooses to make the lifesaving gift of organ donation falls victim to discriminatory insurance practices because of that decision. Governor Abbott's signature on this bill will remove barriers for living organ donors and ultimately will save lives by increasing the number of kidneys and other organs available for Texans who are awaiting transplantation."

At the federal level, AKF continues to advocate for the Living Donor Protection Act of 2021 (HR 1255/S 377) that would ensure a uniform baseline of living donor protections nationwide.

NKF Partners with Cryptocurrency Charity

In late May, Elongate, the world's largest charity cryptocurrency hosted a livestream to announce a partnership with the National Kidney Foundation (NKF). The event introduced the **Kevin Longino,** NKF CEO, and **Anthony Tuggle,** board chair, to the cryptocurrency community to share the impact of the work of NKF on patients' lives. Elongate will encourage their community of investors to become involved in the fight against kidney disease.

In a press release, Mr. Longino said, "We are so grateful to Elongate for this exciting collaboration and innovative charitable cryptocurrency community interested in learning more about kidney disease, a public health crisis affecting 37 million adults in the US. This is our first foray into the cryptocurrency space, and we're really excited to build a relationship with Elongate and its community members while also sharing the impact of their support on those living with kidney disease."

Elongate is a cryptocurrency token born from a tweet dated March 25 by Elon Musk. The Elongate team plans to host livestreams with their community investors. At present, Elongate has no affiliations with Elon Musk.

Kidney Disease Education for US Veterans

The American Kidney Fund (AKF) has announced support from Bayer to aid in AKF's efforts to educate US veterans about the key role kidneys play in overall health as well as the importance of early detection to prevent or slow the progression of kidney disease. The collaboration with Bayer builds on the Fund's existing partnership with the US Department of Veterans Affairs Health Administration (VA) to increase awareness of kidney disease among US veterans and to support veterans who have been diagnosed with kidney disease.

In a press release, **LaVarne A. Burton,** AKF president and CEO, said, "About 500,000 US veterans have kidney disease, and that number continues to trend upward by 6% each year, as it has tor the past five years. We are grateful for Bayer's support of our work to reach out to veterans—a population that faces higher rates of kidney diseases compared to the general public"

Amit Sharma, MD, FACP, FASN, FNKF, vice president of medical affairs, cardiovascular & renal division, Bayer, said, "A major risk factor for chronic kidney disease is type 2 diabetes and many veterans

living with type 2 diabetes do not realize they are at risk. Bayer is proud to support AKF's work to educate America's veterans on kidney disease risk factors, early detection, and disease management, to help all veterans living with kidney disease live healthier lives."

Early Assessment Addresses Treatment Ambiguity in DKD

In a late spring press release, RenalytixAI announced results from a utility study that confirmed the importance of risk assessment testing to address ambiguity in the early stages of diabetic kidney disease (DKD) as well as improving patient engagement and adherence. KidneyIntelX has been shown to accurately predict progression of DKD.

In results of the qualitative study that involved 16 primary care physicians, 100% of study participants confirmed that early-stage kidney risk assessment, such as that provided by KidneyIntelX, will help address suboptimal therapy.

Joseph Vassalotti, MD, chief medical officer of the National Kidney Foundation (NKF) and clinical professor at the Icahn School of Medicine Mount Sinai Health System, said, "The NKF believes primary care physicians have the power to change the outcome for the vast majority of individuals with early-stage kidney disease who are at risk for progressive kidney disease. Americans living with kidney disease universally express the preference for early diagnosis. This study confirms the compelling data presented at this year's NKF Spring Clinical Meeting that KidneyIntelX could be widely adopted by primary care physicians and could alter how at-risk populations with type 2 diabetes can receive early education and therapeutic intervention to reduce DKD complications and kidney failure."

Monogram Announces Funding Round

In late spring, Monogram Health issued a press release to announce $160 million Series B funding led by TPG Capital. Monogram, based in Nashville, Tennessee, works to manage chronic kidney disease and end-stage kidney disease at home. The funding round also includes existing investors Frist Cressey Ventures and Norwest Venture Partners, as well as Humana Inc. and other national and regional investors.

The company partners with health plans to provide their members with a renal care model of clinical managed services, including complex case and disease management, utilization management, and medication therapy management, to help improve patient outcomes and quality of life while reducing costs for the healthcare system.

Monogram's board chairman, **Bill Frist, MD,** said, "Welcoming TPG Capital alongside noted national and regional strategic

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investors further validates our industry leading kidney model of care. We look forward to working with the TPG team as Monogram further solidifies its role as the preeminent leader in personalized, compassionate, and evidence-based kidney care for patients."

Mike Uchrin, CEO of Monogram Health, added, "Despite more that 20% of all Medicare spending going toward Americans with kidney disease, the population continues to grow and experience often dismal health outcomes and quality of life. Our model of care dramatically improves health outcomes and reduces spending by delivering the care and services these individuals truly need and want, right in their own homes. One by one, our patient successes are adding up to significant value for our partners, and driving accelerated demand for our services."

Print-only Content

Improving Health Equity in Kidney Transplantation

In an early summer press release, DaVita Kidney Care and the National Kidney Foundation (NKF) announced the launch of The Big Ask: The Big Give, a pilot program aimed at improving health equity in kidney transplantation. The pilot will launch in Colorado, New York, Minnesota, and New Mexico. Both DaVita and NKF have strong presence in those states, and have operational teams that are well connected to the transplant and healthcare ecosystem.

Kevin Longino, NKF CEO, said, "Many people never find a living donor simply because they are afraid to ask. NKF's The Big Ask: The Big Give platform helps patients and families learn how to find a living donor and we are grateful to DaVita for their support in helping to reach patients in underserved areas."

The platform offers support and tools in a virtual format. NKF provides patents and families seeking a kidney transplant from a living donor in-depth education and support, including one-on-one guidance from a trained Patient Navigator, interactive tools on a new web platform, a private online community for program participants, and support from healthcare professionals.

Jeff Giullian, MD, chief medical officer for DaVita Kidney Care, said, "Finding a living kidney donor is a big deal. NKF's The Big Ask: The Big Give program is a tremendous resource to empower patients with the knowledge and confidence to spread the word about their need and have these deeply personal conversations. We hope that combining NKF's innovative program with DaVita's expertise in care delivery will improve health equity among patients receiving transplants from living donors in this pilot."

Leadership Hires at Renalytix™ Announced

In a recent press release, Renalytix™ AI announced a slate of leadership hires to aid in the expanding deployment of KidneyIntelX™ to government agencies and healthcare providers. The new hires include **Missy Martin-Kemp,**

vice president of sales, Eastern US, who will recruit and lead a team of sales representatives to support primary care physician and specialist practices who utilize KidneyIntelX testing; **Christine Loftsgaarden,** vice president of commercial partnerships, who will focus on expanding collaborations with health systems, federal government agencies, and payers to implement integrated care solutions based on KidneyIntelX risk assessment in early stage diabetic kidney disease.

Stacey Molinari has joined the commercial team as director of commercial partnerships in the northeast region. She will work to expand the Mount Sinai KidneyIntelX program to other regional and government owned health systems. **Jon Wisson** is joined the managed care team as senior manager, government access and will head contracting efforts with Veterans Affairs centers and regional networks.

Andria Parks-Herrera is vice president of marketing at Renalytix AI. She will direct communications across provider, payer, and patient stakeholder groups and work to advance private and government partnerships focused on education, care delivery, and patient engagement in support of adoption of KidneyIntelX.

NKF Kidney Research Connect

The National Kidney Foundation has announced the creation of NKF Kidney Research Connect, a portal to connect kidney patients, care partners, and living donors with researchers to collaborate on patient-centered outcomes research.

In a press release, **Kerry Willis, PhD,** chief scientific officer at NKF, said, "Our main goal is to build the kidney community's ability to engage as partners in patient-centered outcomes research and comparative effectiveness research by improving the knowledge of the patient-centered research process among investigators, patients, and other stakeholders and providing a platform to connect patients and researchers. We couldn't be more optimistic that Kidney Research Connect will not only do that but also drive an increase in patient-centered outcomes research within the kidney community."

Kidney patients and care partners can sign up to receive information about upcoming prospective patient-centered research projects by going to www.kidney.org/research-connect. Researchers can register and add their prospective investigations to the site and be connected with registered patients who meet their project criteria.

CARE for All Kidneys Act of 2021

Rep. Lisa Blunt Rochester (D-DE) and Brad Wenstrup (R-OH) introduced the Coordination, Accountability, Research and Equity for All Kidneys Act of 2021 (CARE for All Kidneys Act of 2021 [HR 3893]) in early summer. The bill aims to create a national action plan to address kidney disease in underserved populations, including minority and rural communities.

In a press release form the American Kidney Fund (AKF), **LaVarne A. Burton,** president and CEO of AKF, said, "AKF is proud to have worked closely with Reps. Blunt Rochester and Wenstrup to develop a bill that aims to improve the healthcare delivery system, making it more equitable, accessible, and inclusive, and to ensure high quality care for all kidney disease patients. The CARE for All Kidneys Act of 2021 would create a national action plan that brings together key stakeholders, including the National Institutes of Health, the National Institute of Diabetes and Digestive and Kidney Disease, and the Centers for Disease Control and Prevention to address health disparities in kidney disease. The bill would support initiatives like expanding ongoing kidney disease research and addressing lower kidney transplantation rates in underserved communities.

"This legislation is vital in addressing health disparities, improving the social determinants of health in the US and ensuring that all kidney patients have access to the care they need. The introduction of this bill is just the first step. AKF is urging other members of Congress to cosponsor this important legislation to help it advance." ■

Abstract Roundup

COVID-19

Antibodies in Hemodialysis Patients after COVID-19

Journal of the American Society of Nephrology. 2021;32(5):1033-1036

There are few data available regarding the humoral response against severe SARS-CoV-2 infection, including dynamics over time, among patients on maintenance hemodialysis. **Hamza Sakhi, MD,** and colleagues conducted a retrospective study to examine initial and long-term humoral response against SARS-CoV-2 in a hemodialysis population. The researchers evaluated findings from SARS-CoV-2 IgG serologic assays targeting the nucleocapsid antigen or spike antigen up to 6 months of follow-up in patients on hemodialysis in the Paris, France, region who had recovered from COVID-19.

Of the 83 patients in the analysis, median age was 65 years, 71% (n=59) were male, and 34% (n=28) had presented with severe COVID-19. At a median of 67 days postdiagnosis, the researchers observed positive initial SARS-CoV-2 IgG antinucleocapsid serology in 74 patients (89%). In multivariable analysis, immunocompromised status was the only factor significantly associated with lack of an IgG antinucleocapsid antibody response.

For 60 of the 74 patients with positive antinucleocapsid antibody response, 6-month follow-up data were available; 15 patients (25%) had negative antinucleocapsid serology at month 6. Fourteen of 15 sera were tested for antispike antibodies; three of the 14 (21%) were also negative.

Overall, 97% of antinucleocapsid-antibody-positive specimens were also antispike-antibody positive. In multivariable analyses, there were independent associations between female sex, age >70 years, and nonsevere clinical presentation and faster IgG antinucleocapsid titer decay. Following adjustment for sex and age >70 years, the only factor associated with faster decay of IgG antispike antibodies was nonsevere clinical presentation.

In conclusion, the researchers said, "This study characterizes evolution of the SARS-CoV-2 antibody response in patients on hemodialysis and identifies factors that are associated with lack of seroconversion and with IgG titer decay."

Post-COVID-19 Rehabilitation for Patients with CKD

Renal Replacement Therapy. 2021; volume 7, article number:33

Patients with COVID-19 disease from SARS-CoV-2 infection often experience renal complications. COVID-19 patients with chronic kidney disease are at increased risk for a negative prognosis. The SARS-CoV-2 main sequelae in patients with CKD are incomplete recovery of kidney function, muscle weakness and atrophy, breathiness, tiredness, pulmonary fibrosis, and initiation of renal replacement therapy.

According to **Heitor S. Ribeiro, MSc,** "Chronic kidney disease patients infected with SARS-CoV-2 should be monitored by rehabilitation professionals as the cardiopulmonary, musculoskeletal, and cognitive systems might be deteriorated. Long-term consequences of SARS-CoV-2 are unknown and preventive rehabilitation may attenuate them."

The author presented a review designed to provide a theoretical basis for early improvements of physical function health in patients with all stages of CKD by rehabilitation therapies.

CHRONIC KIDNEY DISEASE

Treating Metabolic Acidosis with Base-Producing Fruits and Vegetables

Journal of Renal Nutrition. 2021;31(3):239-247

Guideline-recommended treatment for metabolic acidosis in patients with chronic kidney disease is sodium-based alkali. According to **Nimrit Goraya, MD**, and colleagues, treatment with base-producing fruits and vegetables (F+V) may yield more and improved health outcomes, and provide a cost-effective intervention.

In post hoc analysis of data from a clinical trial, 108 macroalbuminuric, nondiabetic, participants with stage 3 CKD and metabolic acidosis were randomized to one of three groups: (1) group receiving treatment with F+V (n=36) calculated to reduce dietary acid by half; (2) group receiving oral sodium bicarbonate (HCO_3—, n=36) 0.3 mEq/kg body weight/day; and (3) group receiving usual care (n=36), assessed annually for 5 years.

Mean overall health scores were 1 for improved, 0 for no change, and –1 for worsened at 5 years for plasma total CO_2, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, change in medication dose (reduction=1, increased=–1, no change=0), and 1 for met goal and 0 for not meeting goal for estimated glomerular filtration rate (>30 mL/min/1.73 m^2) and systolic pressure (<130 mm Hg). The analysis also examined the number of participants with cardiovascular disease events (myocardial infarctions and strokes), and group medication and hospitalization costs.

At 5 years, there was no difference in net plasma total CO_2 increase between the group treated with F&V and the group treated with HCO_3—. At 5 years, the average health scores differed among the three groups (P<.01), with F+V being descriptively larger than HCO_3— and usual care. There were also differences among the groups in the number of participants experiencing cardiovascular disease events, with none in the F+V group, six in the usual care group, and two in the HCO_3— group. There were differences in total 5-year household cost per beneficial health outcome among the groups (P=.005); usual care had the highest cost and HCO_3— and F+V were comparable.

In summary, the authors said, "Metabolic acidosis improved comparably with F+V or standard oral $NaHCO_3$, but F+V yielded ancillary beneficial health outcomes, fewer participants with adverse cardiovascular events, and per-household cost that was comparable to $NaHCO_3$."

Blood Pressure Control in Young Adults with CKD

Journal of the American Society of Nephrology. 2021;32(5):1200-1209

In middle-aged or older adults with chronic kidney disease (CKD), blood pressure control is a modifiable intervention for cardiovascular events and progression of CKD. However, according to **Alexander J. Kula, MD,** and colleagues, there are limited data available on the association between blood pressure and outcomes in young adults with CKD.

The researchers conducted an observational study among 317 young adults 21 to 40 years of age with mild-to-moderate CKD who were enrolled in the CRIC (Chronic Renal Insufficiency Cohort) study. Exposures included baseline systolic blood pressure evaluated continuously (per 10 mm Hg increase) and in categories (<120, 120-129, and ≥130 mm Hg). Primary outcomes of interest were cardiovascular events (heart failure, myocardial infarction, stroke, or all-cause death), and progression of CKD (defined as 50% decline in estimated glomerular filtration rate or end-stage kidney disease). Associations between baseline systolic blood pressure and cardiovascular events and CKD progression were examined using Cox proportional hazard models.

Of the 317 study participants, 52 had a cardiovascular event and 161 had CKD progression during median follow-up times of 11.3 years and 4.1 years, respectively. In the subgroup with baseline systolic blood pressure ≥130 mm Hg, 3% per year developed heart failure, 20% per year had progression of CKD, and 2% per year died.

In fully adjusted models, there were significant associations between baseline systolic blood pressure ≥130 mm Hg (versus systolic blood pressure <120 mm Hg) and cardiovascular events or death (hazard ratio [HR], 2.13; 95% confidence interval [CI], 1.05-4.32) and progression of CKD (HR, 1.68; 95% CI, 1.10-2.58).

In conclusion, the researchers said, "Among young adults with CKD, higher systolic blood pressure is significantly associated with a greater risk of cardiovascular events and CKD progression. Trials of blood pressure management are needed to test targets and treatment strategies, specifically in young adults with CKD."

DIABETES

Mortality Rates among Transplant Recipients with Diabetes

BMJ Open Diabetes & Research Care. doi:10.1136/bmjdrc-2020-001962

There are few data available on the role diabetes type 1 and type 2 plays in modifying prognosis in kidney transplant recipients. **Jessica Harding, MD,** and colleagues conducted a study to compare mortality among kidney transplant recipients with type 1 diabetes, type 2 diabetes, and non-diabetes-related end-stage kidney disease (ESKD).

The study included 254,188 first-time single kidney transplant recipients ≥18 years of age who were identified from the US Renal Data System database (2000-2018). *International Classification of Diseases, 9th and 10th Clinical Modification* codes were used to define diabetes status as primary cause of ESKD. The risk of death associated with type 1 and type 2 diabetes relative to non-diabetes was calculated using multivariable Cox regression models (right-censored). Trends in standardized mortality ratios (SMRs) (2000-2017), relative to the general US population, were assessed using Joinpoint regression.

Median survival time was 14.6 years, over which 72,175 (28.4%) deaths occurred. Five-year survival probabilities were 88% for non-diabetes, 85% for type 1 diabetes, and 77% for type 2 diabetes. Following adjustment, mortality was highest in the type 1 diabetes group (hazard ratio [HR], 1.95; 95% confidence interval [CI], 1.88-2.03) and then type 2 diabetes (HR. 1.65; 95% CI, 1.62-1.69), as compared with non-diabetes.

SMRs declined for all three groups. The SMRs in 2017 were 2.38 (95% CI, 2.31-2.45) for non-diabetes, 6.55 (95% CI, 6.07-7.06) for type 1 diabetes, and 3.82 (95% CI, 3.68-3.98) for type 2 diabetes.

The researchers said, "In the USA, diabetes type is an important modifier in mortality risk among kidney transplant recipients with highest rates among people with type 1 diabetes-related ESKD. Development of effective interventions that reduce excess mortality in transplant recipients with diabetes is needed, especially for type 1 diabetes."

Diabetes and CKD and Quality-of-Life

Nephrology Dialysis Transplantation. 2021;36(6):1048-1056

Chronic kidney disease (CKD) and diabetes are associated with decreased quality-of-life. The combined impact of having both diseases is less well known. **Melanie L. R. Wyld, MBBS, MBA, MPH,** and colleagues conducted a prospective, longitudinal cohort study to measure quality-of-life in patients with both CKD and diabetes.

The study included community-based Australians ≥25 years of age who participated in the Australian Diabetes, Obesity and Lifestyle study. The physical component summary and mental component summary subscores of the Short Form (36) Health

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Survey were used to measure quality-of-life.

A total of 11,081 participants had quality-of-life measurements at baseline. Of those, 1112 had CKD, 1001 had diabetes, and 271 had both. Of the patients with CKD, 421 had CKD stage 1, 314 had stage 2, 346 had stage 3, and 31 had stages 4/5. Baseline physical component summary scores were lower for those with both CKD and diabetes than those with either disease alone ($P<.001$) in adjusted linear mixed effect models. In longitudinal analyses, there was a more rapid decline in physical component summary score in those with both diseases.

In conclusion, the researchers said, "The combination of CKD and diabetes has a powerful adverse impact on quality-of-life, and participants with both diseases had significantly poorer quality-of-life than those with one condition."

DIALYSIS

Recovery of Kidney Function in Patients on Maintenance Dialysis

Nephrology Dialysis Transplantation. 2021;36(6):1078-1087

Researchers, led by **Lily Jakulj, MSc,** conducted a study designed to examine the incidence of recovery of kidney function in patients with end-stage kidney disease treated with maintenance dialysis (>90 days). The study included adult patients from the European Renal Association—European Dialysis and Transplant Association Registry who initiated maintenance in 1997-2016. Sustained recovery of renal function was defined as permanent discontinuation of dialysis. The researchers also evaluated non-sustained recovery of kidney function (≥30 days). Cox regression analysis was used to assess factors associated with recovery of kidney function adjusted for potential confounders.

Of 440,996 patients in the database, recovery of kidney function occurred in 1.8% (n=7657). Of those, 71% experienced sustained recovery of renal function. Approximately 90% of all recoveries occurred within the first 2 years after Day 91 of dialysis. Of the patients with non-sustained recovery of kidney function, 39% reinitiated kidney replacement therapy within 1 year.

There were strong associations between sustained recovery of kidney function and the following underlying kidney diseases (as registered by the treating physician): tubular necrosis (irreversible) or cortical necrosis (adjusted hazard ratio [aHR], 20.4; 95% confidence interval [CI], 17.9-23.1); systemic sclerosis (aHR, 18.5; 95% CI, 13.8-24.7), and hemolytic uremic syndrome (aHR, 17.3; 95% CI, 13.9-21.6). There were weaker associations for hemodialysis as the first dialysis modality (aHR, 1.5; 95% CI, 1.4-01.6) and initiation of dialysis at an older age (aHR, 1.8; 95% CI, 1.6-2.0) or in a more recent time period (aHR, 2.4; 95% CI, 2.1-2.7).

"Definitive discontinuation of maintenance dialysis is a rare and not necessarily an early event. Certain clinical characteristics, but mostly the type of underlying kidney disease, are associated with a higher likelihood of recovery of kidney function," the researchers said.

PEDIATRIC NEPHROLOGY

PEW IN PEDIATRIC CKD and ESKD

Journal of Renal Nutrition. 2021;31(3):270-277

Protein energy wasting (PEW) is a nutritional comorbidity associated with increased mortality. According to **Arpana Lyengar, MD, DNB, FPN, FRCP,** and colleagues, PEW is under-recognized in children with chronic kidney disease (CKD). The researchers conducted a study to identify the burden and factors associated with PEW and to examine the utility of parameters used to diagnose PEW in children with CKD and end-stage kidney disease (ESKD).

Over a 30-month period, the researchers recruited children 2-18 years of age with CKD stages 2 to 5. The assessed parameters of PEW were body mass index for height, mid-upper circumference, height for age, appetite, serum albumin, cholesterol, transferring, and C-reactive protein. PEW was stratified as mild, standard, and modified PEW, based on the number of criteria fulfilled in each patient.

A total of 123 children were recruited. The male to female ratio was 3:1. Of the total cohort, 73 had CKD stages 2 to 4 and 50 had ESKD. PEW was identified in 58% of the cohort: 47% in CKD stages 2 to 4 and 73% of those with ESKD, $P=.035$. There were associations between Pew and longer duration and severity of disease.

The most useful criteria for the diagnosis of PEW were reduced appetite ($P=.001$ in CKD stages 2-4 and $P=.04$ in ESKD), low mid-upper arm circumference ($P=.000$ in CKD stages 2-4 and $P=.006$ in ESKD), and low body mass index for height ($P=.000$ for CKD stages 2-4 and $P=.007$ for ESKD). Most children did not meet biochemical criteria. Inflammation was higher in the ESKD group than in the CKD stages 2-4 group (59% vs 39%, respectively; $P=.02$), but was associated with PEW only in CKD stages 2-4.

In summary, the researchers said, "PEW was highly prevalent in children with CKD and ESKD. Appetite and anthropometry measures were more useful than biochemical criteria for diagnosis of PEW. Whereas inflammation was common, it was associated with PEW only in CKD stages 2-4. Pediatric CKD and ESKD may need exclusive diagnostic criteria for PEW based on anthropometry, appetite, and inflammation." ■

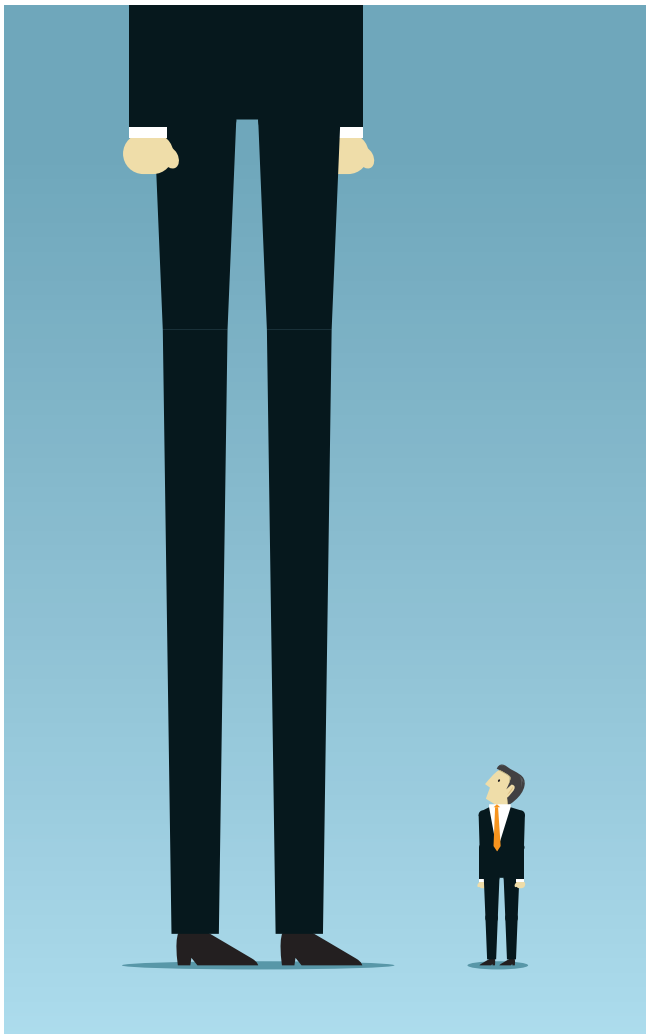
Sarah Tolson

Independent Dialysis Programs: An Underdog story

When I began my adventure in renal billing, I was looking for an opportunity to make a meaningful contribution to society. I did not yet understand the dialysis industry and the challenges small dialysis programs and their patients faced each day, but I quickly learned. I felt that the one small thing I could do to ease their burden was to make sure patient claims for dialysis services were paid correctly and benefit issues were handled smoothly.

Over the years, I began to learn about the advantages that the large dialysis organizations (LDOs) have over the small, independent programs that I was used to working with. Due to their size, LDOs can negotiate better purchase rates for medications and supplies, are able to obtain *significantly* better rates with commercial insurance companies, and, in some instances, prevent independent programs from getting contracts with a payer.

I was fortunate enough to learn from dialysis facility staff about the challenges they face in treating their patient populations. My company has worked with dialysis programs that help patients with limited resources get set up with food, housing, and transportation services. This knowledge really drove home the understanding that the small, independent programs I worked with were the underdogs and their patient populations were counting on them to provide the treatment they needed to stay alive.



On the other end of the spectrum are large insurance companies—which, just like dialysis programs and nephrologists, play an integral role in a patient's healthcare. When a patient enrolls with an insurance plan, they agree to follow a set of guidelines and make their premium payments each month and the insurance company agrees to reimburse the medical providers that render medical services covered by the insurance policy. What happens if the patients and dialysis program follow the insurance company's guidelines, but the insurance company refuses to pay?

The dialysis program has an obligation to continue treating the patient because patients with ESRD need dialysis or a transplant to sustain life. Depending on the renal network they are in, it may be difficult to transfer the patient to a different dialysis program. A reader of this column wrote to me recently to ask for guidance on how to resolve a specific situation in the dialysis program where they work. The reader's dialysis facility is in the same building as a well-established nursing home that shares common ownership and is contracted with all area insurance companies. The facility has been Medicare certified for quite some time but has been out of network with some of the large commercial payers that administer Medicare Advantage plans in their area. While working to get contracted with these large commercial payers, the facility has been careful to only admit patients to the dialysis unit that have out-of-network benefits. When the facility began submitting claims to the commercial payer that insured the largest portion of the dialysis program's Medicare Advantage patients, they received denials requesting copies of documentation the insurance needed to load the dialysis facility into their system. After submitting the requested documentation, the dialysis program expected that their claims would be reimbursed. Instead, the insurance company denied the claims a second time and requested different documentation.

These denials continued for months but eventually the facility was successful in escalating their problem to a supervisor at the insurance company. Much to the surprise of the dialysis facility, the supervisor claimed that their hands were tied, and they were unable to process any of the dialysis facility's claims due to a system issue outside of their control. When the dialysis facility asked the claims supervisor what could be done, the supervisor told them that the system issue needed to be resolved yet offered no further guidance. This situation has left the dialysis facility without reimbursement from the insurance company for nearly two years.

Unfortunately, situations like this happen to small independent dialysis programs and nephrologists more often than they should. If you are a small dialysis program or small provider and are struggling with a difficult reimbursement situation, know the requirements the insurance company has for disputing denied claims and follow them, document your actions in resolving the denied claims and continue to escalate the issue until it receives the attention of someone who can resolve the problem. If you are an insurance company in receipt of claims from a small dialysis program, do the right thing and pay the claims if they meet your guidelines for coverage. ■

Sarah Tolson is the director of operations for Sceptre Management Solutions, Inc., a company specializing in billing for outpatient ESRD dialysis programs, nephrology practices, and vascular access. Your questions are welcome, and she can be reached at stolson@sceptremanagement.com, 801.775.8010, or via Sceptre's website, www.sceptremanagement.com.

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