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Practical News, Trends, and Analysis

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Pain Protocol Minimizes Opioid Use After Kidney Transplant

Between 2009 and 2019, nearly 500,000 people in the United States died of opioid overdoses. Nearly 247,000 of those deaths involved a prescription opioid, with an average of 37 deaths per day. Following a declaration from the US government in 2017 identifying the opioid epidemic as a public health emergency and outlining a five-point strategy to combat the crisis, the past few years have seen a decline in prescription opioid overdose deaths.

Data have shown that more than 80% of patients undergoing low-risk surgery receive perioperative opioids. Three large registry analyses revealed an association between perioperative opioid use and increased risk of adverse outcomes, including graft failure, and death in graft recipients; however, there appears to be a dose- and exposure-associated increase in risk. Results of a large cohort study of kidney transplant recipients suggested that there may be an association between long-term prescription opioid use and an increased risk of death and graft loss compared with no or short-term opioid prescriptions.

In 2018, the Medical University of South Carolina, Charleston, implemented a quality improvement project that included a multidiscipline, multi-modal pain regimen and education process (MMPREP) to minimize opioid use after kidney transplantation. Early results indicated a reduction in opioid exposure

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Extreme Heat Exposure and Renal Emergency Department Visits

Mortality and morbidity associated with kidney disease are responsible for substantial public health and economic burdens worldwide. Kidney disease is also a key determinant of poor outcomes for other noncommunicable diseases (NCDs), with 7.6% of the 1.4 million annual cardiovascualr deaths attributed to decreased kidney function. Kidney disease, diabetes, hypertension, and cardiovascular disease have profound impacts on global morbidity and mortality, yet kidney disease receives less attention in research on the treatment and etiology of NCDs, according

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Intradialytic Exercise and Patient Survival

The prevalence of chronic kidney disease (CKD) is increasing, leading to an exponential increase in the number of patients progressing to kidney failure requiring kidney replacement therapy (KRT); hemodialysis, peritoneal dialysis, or kidney transplantation. Worldwide, the most common treatment modality is hemodialysis, accounting for 69% of all KRT and 89% of all dialysis. Compared with individuals with normal kidney function, those receiving hemodialysis have higher rates of functional impairment, morbidity, hospitalization, and mortality.

According to **Mohammad Ali Tabibi, PhD,** and colleagues, adverse outcomes among individuals on hemodialysis are associated with low physical activity due to high rates of comorbidities, protein energy wasting, sarcopenia, decreased physical function, decreased aerobic capacity, enforced inactivity during weekly hemodialysis sessions, and postdialysis fatigue. The activity rates of patients receiving hemodialysis are between 20% to 50% that of healthy counterparts.

The researchers conducted a randomized, controlled trial in a hemodialysis center in Iran to examine the effect of intradialytic exercise on survival. The study also sought to assess the effect of intradialytic exercise on clinical outcomes associated with patient survival. Results were reported online in *BMC Nephrology* [doi.org/10.1186/s12882-023-03158-6].

The primary outcome measure was 1-year survival. Secondary outcome measures included changes in serum albumin, hemoglobin, hematocrit, red blood cell count, serum calcium, serum phosphorous, and parathyroid hormone over time.

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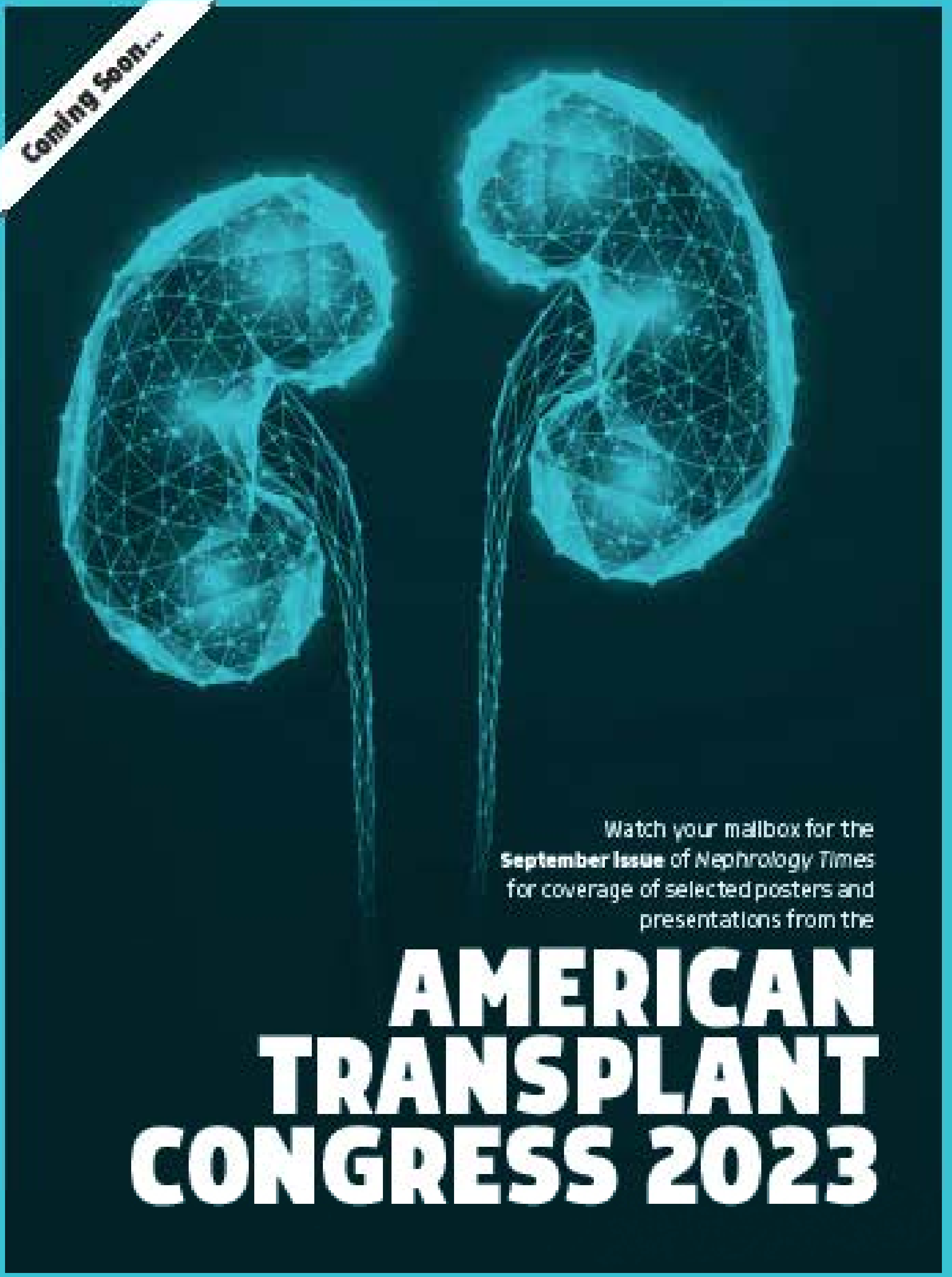

Watch your mailbox for the
September Issue of Nephrology Times
for coverage of selected posters and
presentations from the

AMERICAN TRANSPLANT CONGRESS 2023

SGLT2 Inhibitors and CKD

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Sodium-glucose cotransporter 2 (SGLT2) inhibitors are impressively effective in patients with chronic kidney disease (CKD)—treating hyperglycemia in those patients with type 2 diabetes, reducing blood pressure, slowing kidney progression, and reducing the risk of heart failure.[1,2] SGLT2 inhibitors are well tolerated and on the cusp of becoming generic medications, which could make them much less expensive and much more available.

In a recent article published in *Nature* titled "SGLT2 inhibitors breathe life into kidney-disease care,"[3] Amanda Keener reviews the potential use of SGLT2 inhibitors in all patients with CKD, from children to adults, and potentially even in high-risk CKD patients with type 1 diabetes. Can SGLT2 inhibitors be used in all patients with CKD?

The most important group of patients who should receive treatment with SGLT2 inhibitors is patients with CKD and type 2 diabetes. These patients represent 30% to 40% of all patients with CKD. Multiple trials have demonstrated benefit in slowing progression of kidney disease and reducing the rate of heart failure hospitalization.[1,2,4] However, the evidence that all patients, including those with normo- or microalbuminuria have renoprotective benefits from SGLT2 inhibitors is quite limited.[5]

Should all patients across the etiologic spectrum of CKD be treated? The evidence from both the DAPA-CKD and EMPA-Kidney studies suggests that the answer is probably yes. Approximately 25% of patients recruited in the DAPA-CKD trial and about 66% of patients in the EMPA-Kidney trial did not have diabetes and yet showed renal and cardiovascular benefit from SGLT2 inhibitors. However, there is no definitive evidence that patients with transplant immunosuppression-related CKD benefit from SGLT2 inhibitors,[6] largely because renal transplant patients were excluded from the pivotal SGLT2 inhibitor trials. A retrospective study in transplant recipients supported efficacy in treating hyperglycemia and hypomagnesemia but did not evaluate renal or cardiovascular end points.[7] Likewise, it is not clear whether patients with autosomal-dominant polycystic kidney disease and other renal genetic disease would benefit from SGLT2 inhibitors.[8]

Whether SGLT2 inhibitors can be used in children is also a bit uncertain. While type 2 diabetes mellitus (T2DM) is not common in children and adolescents, the number of patients with T2DM in this age group is increasing. Further, SGLT2 inhibitors are effective in slowing nondiabetic CKD. In 2021, the European Medicines Agency approved SGLT2 inhibitors in children older than 10 years of age. In the United States, approval for use of SGLT2 inhibitors in children with CKD is pending.

There are patients in whom SGLT2 inhibitor treatment is contraindicated. Patients with CKD from type 1 diabetes mellitus (T1DM) should not receive SGLT2 inhibitor treatment. This is due to the risk of euglycemic ketoacidosis (commonly defined as ketoacidosis with a blood sugar <250 mg/dL). The mechanism is thought to involve insulinopenia and increased glucagon secretion, both leading to increased lipolysis and ketogenesis.[9]

Trials studying SGLT2 inhibitors in T1DM patients show an increased risk of diabetic ketoacidosis (DKA). In the inTANDEM trial in T1DM, the SGLT2 inhibitor sotagliflozin was effective in treating hyperglycemia but associated with a dose-dependent three- to five-fold higher rate of DKA.[10] Similar results were observed in the DEPICT-2 trial using dapafliglozin.[11] The US Food and Drug Administration estimates that for every 26 patients with T1DM receiving treatment with an SGLT2 inhibitor, there will be one case of DKA, translating into 16 additional deaths in the United States each year.[12] Ultimately, it is likely that the risk-benefit of SGLT2 inhibitors in patients with CKD will need to be weighed. Whether the trade-offs for treatment favor SGLT2 inhibitor use in patients with CKD with T1DM remains uncertain.[3]

SGLT2 inhibitors are contraindicated in pregnancy, especially during the second and third trimesters, because of concerns about toxicity observed in animal studies. Some concern has also been expressed about using SGLT2 inhibitors in breastfeeding mothers, although the evidence for harm is more theoretical because SGLT2 inhibitors are not secreted into breast milk. Nonetheless, the manufacturer of dapafliglozin, among others, does not recommend use in breastfeeding mothers.

In addition to specific subpopulations of patients with CKD, SGLT2 inhibitors should be used cautiously in patients who are sick or have limited oral intake. Wang et al[9] reinforce guideline recommendations[13] that SGLT2 inhibitors be held at least 24 hours before and for at least 3 to 4 days after elective surgery, invasive procedures, and anticipated severe stressful physical activity. This is because the pharmacologic effects of SGLT2 inhibitors persist beyond five half-lives of elimination (2-3 days).

The bottom line is that SGLT2 inhibitors are breathing life into slowing kidney progression and reducing cardiovascular complications in patients with CKD. However, more research is needed to demonstrate their efficacy and safety in key subpopulations. ■

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Extreme Heat Exposure
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to **Yanji Qu, MD, PhD,** and colleagues.

Climate change is playing an increasing role in the global burden of kidney disease. Previous studies have shown associations between extreme heat exposure and increased incidence, morbidity, and hospital admission rates for kidney disease. Other studies have examined the associations between extreme heat exposure and emergency department (ED) visits for kidney disease overall, as well as subtypes, including acute kidney injury (AKI), chronic kidney disease (CKD), kidney stones, urinary tract infections (UTIs), and renal colic.

According to the researchers, collective results of those studies are inclusive and current understanding of the specific impact of extreme heat exposure on kidney disease is limited. The researchers conducted a case-crossover study to fill knowledge gaps in the associations between extreme heat exposure and renal ED visits. Results were reported in the *American Journal of Kidney Diseases* [2023;81(5):507-516].

The study examined the associations between extreme heat exposure and ED visits related to kidney disease overall and by subtype in summer and transitional months in New York state. To further define associations between extreme heat exposure and ED visits, data were stratified by sociodemographic characteristics.

Extreme heat exposure was defined as when the daily temperature exceeded the 90th percentile temperature of that month during the study period in the county. The outcome of interest was ED visits with a principal diagnosis of kidney disease and its subtypes *(International Classification of Diseases, Ninth Revision* codes 580-599, 788).

A conditional logistic regression model, controlling for humidity, air pollutants, and holidays, was used to compare extreme heat exposure on the ED visit days with extreme heat exposure on control days. The excess risk of kidney disease was calculated for a week (lag days 0-6) after extreme heat exposure during the warm season (May through September).

There were 1,114,322 ED visits related to kidney disease in New York state during the study period. Overall, temperature and the number of kidney-related ED visits were highly correlated. During the months May to September, there was a monotonically increasing risk of renal ED visits as temperatures increased. Depending on the day, there was an association between extreme heat exposure and a 1.7% (95% CI, 0.9%-2.5%) to 3.1% (95% CI, 2.3% to 4.0%) excess rate of kidney-related ED visits in the week following the exposure. The impact of extreme heat exposure on kidney-related visits to the ED increased from lag day 0 to lag day 2, weakening after the strongest effect on lag day 2.

In general, the association between extreme heat exposure and kidney-related ED visits was stronger in the transitional months (excess rates ranged from 1.8% to 5.1%) than in summer (excess rates ranged from 1.5% to 2.7%). In May, the association between extreme heat exposure and kidney-related ED visits persisted for a week after the exposure; the strongest association occurred on lag day 2 (excess rate of 5.1%; 95% CI, 3.4%-6.8%). In September, the strongest association was on lag day 0 (excess rate of 4.2%; 95% CI, 2.6%-5.8%). A statistically significant association was lost by lag day 4.

There were significant associations between extreme heat exposure and greater ED visits due to AKI, kidney stones, UTIs, other kidney and ureter disorders, and other lower urinary tract disorders. The association was strongest for AKI and lasted for 4 days following the extreme heat exposure. The association with kidney stones persisted for a week, and the association with UTI was transient and lasted from lag day 0 to lag day 2.

The association between extreme heat exposure and kidney-related ED visits was significantly modified by age and sex. Individuals >65 years of age experienced more kidney-related ED visits during the short-term period after extreme heat exposure (from lag day 0 to lag day 3). For those 18 to 65 years of age and 5 to 18 years of age, the association between extreme heat exposure and excess risk of renal ED visits lasted the week following the exposure (lag day 0 to lag day 6). The association was stronger for males than for females.

There were no significant associations between extreme heat exposure and the risk of renal ED visits based on race, ethnicity, and insurance status. Excess rates of kidney-related ED visits were assessed according to the number of days of extreme heat exposure during the week prior to the visit to detect a potential dose dependence. The association between extreme heat exposure and kidney-related ED visits showed a dose-dependent trend from 1 to 5 days of exposure in the previous week; the trend did not persist beyond 5 days of exposure.

The researchers noted some limitations to the study findings, including the sample size in the analyses of the associations between extreme heat exposure with subtypes of kidney disease, the possibility of confounders, limiting the analyses to the severe cases of kidney disease, not evaluating individual exposure to heat or access to air conditioning, and the possibility of exposure misclassification due to assigning the same temperature values for a specific day for cases within a county.

In conclusion, the authors said, "Extreme heat exposure was significantly associated with increased risk of ED visits related to multiple kidney disease types and displayed a dose-dependent relationship. This association lasted a week after exposure and was stronger during transitional months (especially May) than in summer. The kidney disease subtype showing the strongest association was AKI, although kidney stones and UTIs also showed strong associations. Age and sex may modify observed associations. The association of extreme heat exposure and kidney disease was observed not only in summer but also in transitional months." ■

TAKEAWAY POINTS

- Researchers reported results of a case-crossover study assessing the associations between extreme heat exposure and kidney-related emergency department (ED) visits in summer and transitional months in New York state.
- There was an association between extreme heat exposure and a 1.7% (lag day 0) to 3.1% (lag day 2) higher risk of kidney-related ED visits.
- The association was stronger in the transitional months (May and September) and was strongest among ED visits related to acute kidney injury, kidney stones, and urinary tract infections.

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Intradialytic Exercise

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Also of interest were physical function and nutritional status.

Physical function was evaluated with the 6-minute walk test, performed according to the American Thoracic Society guidelines. The test weas performed on a 30-meter straight course. Participants were asked to walk as fast as possible for 6 minutes. Walking aids were allowed and recorded. Distance was measured at the end of the 6-minute period. Nutritional status was assessed by Geriatric Nutritional Risk Index.

Intervention adherence was defined as the number of sessions performed divided by the number of sessions offered, multiplied by 100. The adherence rate was 81%.

structive pulmonary disease, gastrointestinal bleeding, liver disease, cancer, and diabetes).

Patients were randomized 1:1 to either the intervention group or the control group. Those in the intervention group performed concurrent intradialytic exercise during the second hour of dialysis (60-minute exercise sessions three times a week) for 6 months. The intervention was a combination of aerobic and resistance exercises. Exercises were individualized to match participants' level of physical fitness. Participants in the control group did not undertake any specific physical activity during dialysis. Follow-up for all participants was 12 months.

Of the 95 patients assessed for eligibility, 74 met eligibility criteria and were randomized. During the study period, two participants in the intervention group and four in the control group were excluded. Every patient who was

> The cumulative survival rate in the control group was significantly lower than that in the intervention group (log rank statistics=6.5, *P*=.01).

Prior to study initiation, educational and motivational posters were installed in the dialysis center to familiarize all patients with the benefits of exercise, particularly intradialytic exercise. Patients were then informed of the side effects of inactivity and a sedentary lifestyle. All eligible patients received a baseline assessment, including demographic characteristics, primary cause of kidney failure, and comorbidities. Comorbidities were quantified using the Charlson Comorbidity Index established for patients on dialysis, including the underlying cause of kidney failure plus 11 comorbidities (atherosclerotic heart disease, congestive heart failure, cerebrovascular accident/transient ischemic attack, peripheral vascular disease, dysrhythmia, and other cardiac diseases, chronic ob-

lost to follow-up (for any reason except death) during follow-up was censored.

The intervention and control groups were balanced in baseline characteristics. In the intervention group, mean age was 62 years, 57% (n=27) were men, and mean dialysis history was 29 months. In the control group, mean age was 65 years, 62% (n=23) were men, and mean dialysis history was 26 months.

During the initial 6-month period when the exercise intervention was being performed, no one in the intervention group died and two participants in the control group died. During the 12-month follow-up period, two participants in the intervention group (6%) died: one due to cardiovascular disease and one due to unknown cause. In the control group, nine participants (27%) died during follow-up: three due to cardiovascular disease, two due to cerebrovascular disease, one due to infection, two due to other causes, and one due to unknown cause. The cumulative survival rate in the control group was significantly lower than that in the intervention group (log rank statistics=6.5, *P*=.01). Results of univariable Cox regression model analyses were similar.

In all secondary outcomes, there were significant between-group changes observed during the 6-month intervention period. Serum albumin, hemoglobin, red blood cell count, serum calcium, physical function, and nutritional status tended to increase in the intervention group, but remained relatively stable in the control group. Serum parathyroid hormone and phosphorous levels significantly decreased in the intervention group, but remained relatively stable in the control group.

During the study period, there were no treatment- or intervention-related serious adverse events. One patient in the intervention group had muscle cramp after two sessions of exercise and one patient had bleeding from fistula while doing the exercises.

In citing limitations to the study findings, the authors included the short duration (6 months) of the intradialytic exercise intervention as well as the short duration (12 months) of follow-up that resulted in the long-term effects of exercise on patient survival remaining uncertain. In addition, the small sample size resulted in an imprecise estimate of the effect of exercise on patient survival, and survival was timed from the end of the intervention, introducing immortal time bias. Finally, the secondary outcome measures assessing the effects of intradialytic exercise and patient survival were only examined during the first 6 months of the study.

"Intradialytic exercise performed for at least 60 minutes during thrice weekly dialysis sessions improves survival in adult patients receiving hemodialysis," the researchers concluded. "Further large-scale studies are warranted." ■

TAKEAWAY POINTS

- Researchers reported results of a study examining the effect of intradialytic exercise on survival in a population of adults receiving maintenance hemodialysis.
- The primary outcome measure was survival rate at 12 months. Secondary outcomes included clinical outcomes associated with patient survival.
- Survival in adults receiving maintenance hemodialysis was improved with intradialytic exercise for at least 60 minutes during thrice weekly dialysis sessions.

Pain Protocol Minimizes Opioid Use

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in the early postoperative period while sustaining appropriate pain control. **Taylor Carcella, PharmD,** and colleagues reported on the long-term durability and effectiveness of the initiative [*JAMA Surgery*. doi10.1001/jamasurg.2023.0276].

The single-center quality improvement study evaluated postoperative and long-term opioid use prior to and following implementation of a MMPREP in adult kidney graft recipients from August 1, 2017, through June 30, 2020. A retrospective chart review was used to collect patient data. Multivariable linear and logistic regression before and after implementation of the program protocol were used to evaluate opioid use up to 1 year following transplant.

The initial cohort included 745 patients who underwent kidney transplant during the study period. The preprotocol group included 96 women and 149 men; mean age was 52.8 years, 59.2% (n=145) were Black, 1.6% (n=4) were Asian, 2.5% (n=6) were Hispanic, 36.3% (n=89) were White, and 0.4% (n=1) were other race and ethnicity. The postprotocol group included 226 women and 272 men; mean age was 52.4 years, 60.2% (n=300) were Black, 2.0% (n=10) were Asian, 1.6% (n=8) were Hispanic, 35.5% (n=177) were White, and 0.6% (n=3) were other race/ethnicity.

Two patients died within 30 days after transplant, resulting in a final analysis cohort of 743 patients. The two cohorts were similar in baseline characteristics. There were no differences in pretransplant morphine milligram equivalent (MME) opioid use per month between the two preprotocol and postprotocol groups (0.15 vs 0.11, respectively; *P*=.19) or in number of patients overall with benzodiazepine use (39 vs 76, respectively; *P*=.82).

There was a statistically significant difference between the two groups in body mass index (postprotocol group, 30.1 kg/m^2 vs preprotocol 29.3 kg/m^2; *P*=.02). The mean date of transplant in the preprotocol group was February 7, 2018 (range, August 3, 2017, to September 2, 2018), and the mean date of transplant in the postprotocol group was August 11, 2019 (range, September 4, 2018, to June 28, 2020). The two groups were similar in donor characteristics.

In the 1-year follow-up in the preprotocol group, the total MME was 1203.7 compared with 581.9 in the postprotocol group. Following implementation of the MMPREP, 34 patients (6.8%) were discharged with an opioid prescription following kidney transplant compared with 236 patients (96.3%) preprotocol (*P*<.001). In the preprotocol group, in-hospital median MME per day was 30.6 mg versus 0.0 mg in the postprotocol group (*P*<.001). Prior to implementation of MMPREP, six patients (2.4%) were opioid free while hospitalized, compared with 199 patients (40%) following protocol implementation (*P*<.001).

Nealy all patients in the postprotocol group received a preoperative nerve block and were discharged with a prescription for gabapentin or pregabalin and acetaminophen. Adherence to protocol components

In the postprotocol group, 313 patients (62.9%) had no opioid use during the 1-year follow-up period, compared with seven patients in the preprotocol group (2.9%).

remained consistent over time. Quadratus lumborum was the most common type of nerve block (405 patients, 81.3%).

During 1-year of follow-up in the preprotocol group, median MME was 450 mg compared with 0 mg in the postprotocol group, including the opioid prescription at time of discharge. In the postprotocol group, 313 patients (62.9%) had no opioid use during the 1-year follow-up period, compared with seven patients in the preprotocol group (2.9%) (adjusted odds ratio [OR], 57.52; 95% CI, 26.55-124.65; *P*<.001). During the follow-up year, patients in the postprotocol group had 99% lower odds of filling opioid prescriptions that totaled more than 100 MME (adjusted OR, 0.01; 95% CI, 0.01-0.02; *P*<.001).

Long-term opioid use was defined as the final 3 months of the follow-up year. During that period, postprotocol patients were one-half as likely to fill two or more opioid prescriptions (OR, 0.52; 95% CI, 0.28-0.99; *P*=.04). In addition, patients in the postprotocol group who were opioid naïve at the time of transplant were half as likely to become long-term opioid users compared with the preprotocol group (OR, 0.44; 95% CI, 0.20-0.98; *P*=.04).

The researchers cited some limitations to the study findings, including the inability to construe the findings as causal due to the study design, the possibility of residual confounding, the use of retrospective data collected as an extension of a previous quality improvement project, the nonrandomized design of the study, and the inability to capture illicit drug use, including opioids.

In conclusion, the authors said, "Results of this long-term, large-scale quality assurance and process improvement endeavor demonstrate a substantial reduction in opioid use in kidney graft recipients associated with the implementation of a multimodal opioid-sparing pain protocol. The protocol was associated with a significant reduction in 1-year postoperative opioid use, including in patients who used opioids at the time of transplant. In opioid-naïve patients, the protocol was associated with a reduced risk of becoming long-term opioid users. A parallel-arm, randomized clinical trial is needed to establish causation and confirm these findings." ■

TAKEAWAY POINTS

- Clinicians reported results of a quality improvement project that included an opioid minimization pain protocol following kidney transplantation.
- An analysis of long-term opioid use among kidney transplant recipients prior to and following implementation of the protocol revealed morphine milligram equivalents during 1-year follow-up of 450 mg and 0 mg, respectively.

Conference Coverage

Austin, Texas | April 11-15, 2023

NATIONAL KIDNEY FOUNDATION

SPRING CLINICAL MEETINGS 2023

Nephrologists, fellows and residents with a special interest in kidney disease, general internists, pharmacists, physician assistants, nurse practitioners, nurses and technicians, social workers, and renal and clinical dietitians all attended the 2023 NKF Spring Clinical Meetings in Austin, Texas, to learn about developments in all areas of nephrology practice and network with colleagues.

Presenters reported the latest insights into chronic kidney disease care and participants were informed about new and evolving concepts related to kidney disease. This is Part Two of our coverage of the meeting.

Blood Transfusion Rates in ASCEND-D and ASCEND-ND Trials

Management of patients with anemia of chronic kidney disease (CKD) seeks to reduce red blood cell transfusions and avoid complications such as allosensitization. Researchers, led by **Vivekanand Jha, MBBS, MD, DM, PhD,** conducted an analysis of data on red blood cell transfusion needs in patients with CKD on and not on dialysis in the ASCEND-D and ASCEND-ND trials. Trial participants were treated with daprodustat, a novel hypoxia inducible factor prolyl hydroxylase inhibitor, or with erythropoiesis-stimulating agents (ESAs).

Results were reported during a poster session at the NKF Spring Clinical Meetings 2023. The poster was titled *The Effects of Daprodustat on Blood Transfusion Rates in the ASCEND-D and -ND Trials.*

The analysis included data on rates of red blood cell transfusions (events per 100 patient-years) in the ASCEND-D and ASCEND-ND trials and in the ASCEND-D ESA hyporesponder (ESA-HR) subgroup (baseline ESA-resistance index >2.0/>450 U/kg epoetin per week). In prespecified analyses, adjustments in Cox proportional model-estimated hazard ratios (HR) included treatment/region, dialysis type in ASCEND-D participants, and randomization-ESA use in ASCEND-ND trial participants.

In both trials, red blood cell transfusions (≥5%) and overall red blood cell transfusion rates were numerically lower in patients in the daprodustat group than in patients in the ESA group. During the evaluation period, there was no difference in time to first red blood cell transfusion for daprodustat versus ESA in ASCEND-D (HR, 0.86; 95% CI, 0.72-1.02; 1-sided *P* value, 0.043) or ASCEND-ND (HR, 0.96; 95% CI, 0.81-1.14; 1-sided *P* value, 0.32). In the ESA-HR subgroup, more participants in the daprodustat group (n=16/183; 9%) than in the ESA group (n=7/180; 4%) had red blood cell transfusions (event rates per 100 patient-years: 39.7 vs 21.4, respectively).

In conclusion, the researchers said, "For daprodustat versus ESA during the evaluation period, few patients received red blood cell transfusions and red blood cell transfusion rates and time to first red blood cell transfusion were similar in ASCEND-D and -ND, and ESA-HRs in ASCEND-D had more red blood cell transfusions."

Source: Jha V, Johansen K, Mallett S, et al. The effects of daprodustat on blood transfusion rates in the ASCEND-D and -ND trials. Poster #183. Abstract of a poster presented during the National Kidney Foundation Spring Clinical Meetings 2023; April 11-15, 2023; Austin, Texas.

Dietary Counseling and Recurrence of Hyperkalemia in Patients With CKD

Previous studies have examined the role of medical nutrition therapy (MNT) in progression of chronic kidney disease (CDK). However, according to **Christopher G. Rowan, PhD,** and colleagues, there are few data available on the relationship between MNT and hyperkalemia.

The researchers conducted a retrospective data analysis in a cohort of adults with stage 3-4 CKD and hyperkalemia (diagnosis of hyperkalemia and serum potassium >5.0 mmol/L) who received MNT from January 1, 2019, to August 31, 2022. Results were reported during a poster session at the NKF Spring Clinical Meetings 2023 in a poster titled *Recurrence of Hyperkalemia Following Dietary Counseling, REVOLUTIONIZE I Real-World Evidence Study.*

The study utilized electronic health record data from TriNetX Dataworks, USA. To focus on patients who received MNT as first-line therapy, those who were treated with oral antihyperkalemia therapy (potassium binder) within 6 months prior to MNT were excluded. Follow-up was censored at the first of 6 months following initiation of MNT, initiation of outpatient therapy with an oral antihyperkalemia therapy, death, or the end date (August 31, 2022).

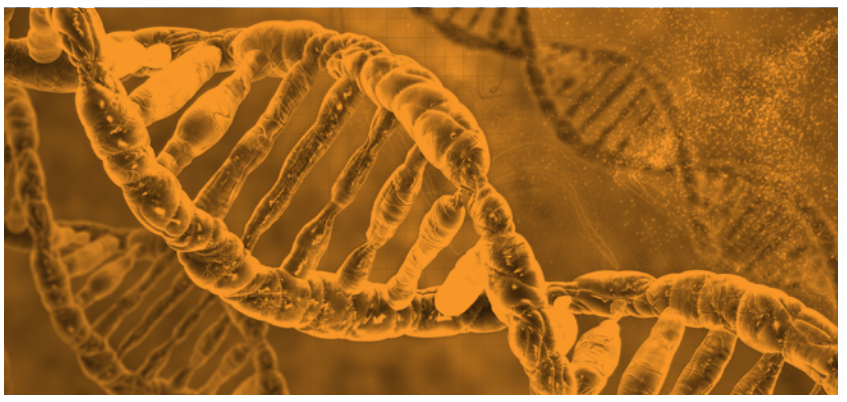
The researchers analyzed the percentage of patients who had a hyperkalemic event at 0-1, 0-2, 0-3, 0-4, 0-5, and 0-6 months following MNT. Using the Chi-square test, during each analysis interval the observed percentage of patients with a recurrence of hyperkalemia was calculated and compared with 50% (the *a priori* estimated hyperkalemia recurrence rate).

The final study cohort included 773 patients. Six months following initiation of MNT, 69% of the cohort (n=532) were uncensored and included in the analysis. Median age at baseline was 70 years, median serum potassium level was 5.4 mmol/L, 59% of the cohort had stage 3 CKD, 41% had stage 4 CKD, 45% were women, 77% were White, and 14% were Black.

The percentages of recurrence of hyperkalemia during the prespecified intervals of 0-1, 0-2, 0-3, 0-4, 0-5, and 0-6 months were: 32.1% ($P<.001$); 39.0% ($P<.001$); 44.9% ($P=.076$); 49.3% ($P=.814$); 52.8% ($P=.367$); and 56.0% ($P=.049$), respectively.

In summary, the authors said, "Within 1 month following MNT nearly one-third of patients had a hyperkalemia recurrence. By 6 months, the majority of patients (56%) had a hyperkalemia recurrence ($P=.049$). To maintain normokalemia and prevent hyperkalemia recurrence among CKD patients, clinicians may augment MNT with a novel oral antihyperkalemia therapy. Additional research is warranted to elucidate these findings."

Source: Rowan CG, Agiro A, Chan A, et al. Recurrence of hyperkalemia following dietary counseling, REVOLUTIONIZE I real-world evidence study. Poster #296. Abstract of a poster presented at the National Kidney Foundation Spring Clinical Meetings 2023; April 11-15, 2023; Austin, Texas.



Improving Diagnostic Precision With Genetic Testing

Monogenic kidney diseases are associated with approximately 10% of occurrences of chronic kidney disease (CKD). According to **Fouad Chebib, MD,** and colleagues, while there are clinical diagnostic criteria available for many renal conditions, there remains a high incidence of misdiagnosis. Genetic testing is available to reclassify or provide an accurate CKD diagnosis, and it can enable personalized disease management.

The researchers conducted a comparison study to describe the utility of genetic findings to confirm, clarify, or reclassify a clinical diagnosis among participants in the RenaCARE study. Results were reported during a poster session at the NKF Spring Clinical Meetings 2023 in a poster titled *The Impact of Genetic Test Results on Kidney Disease Diagnosis.*

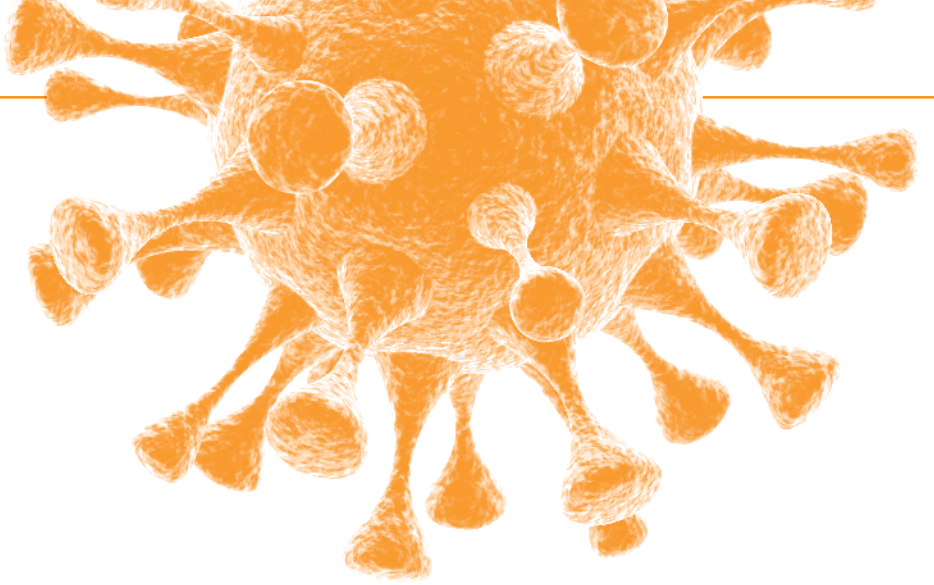
Clinicians provided clinical diagnosis and history for each enrolled patient; the data were compared with results of genetic testing with a next-generation sequencing-based 365-kidney gene panel (the Renasight™ test). Positive genetic results were reported. Clinical history was compared with known results of patients' genetic findings, and the impacts of genetic testing on each clinical diagnosis were identified.

The study enrolled 1624 patients. Mean age was 55 years (range, 18-96 years). The researchers assessed 318 patients with variant(s) in a single gene. Findings from the genetic assessment provided a new or clarified clinical diagnosis for 39.0% (n=124) of those patients and confirmed suspected diagnoses in 33.6% (n=107).

The genetic findings also classified 17.3% of patients (n=55) as at risk for developing illness based on inconsistency between the identified variants and the reported clinical history. Clinical presentation was partially explained by the genetic findings in 5.3% of patients (n=17), and 3.5% (n=11) had a correlation of a clinical diagnosis that also reclassified the category of kidney disease. Finally, in 1.3% of cases (n=4), the genetic diagnosis was consistent with the patients' clinical presentation but was not acknowledged as the disease etiology by the physician.

In conclusion, the authors said, "This study demonstrated that broad-panel genetic testing had significant impacts on patient CKD diagnoses, enabling discernment of diagnosis and presentations that may have been overlooked or misattributed by clinical evaluation alone. The inclusion of genetic findings into CKD evaluation will allow physicians to tailor patient care with improved precision."

Source: Chebib F, Jandeska S, Westemeyer M, et al. The impact of genetic test results on kidney disease diagnosis. Poster #345. Abstract of a poster presented at the National Kidney Foundation Spring Clinical Meetings 2023; April 11-15, 2023; Austin, Texas.



Case Report: Patient With Hypercalcemia Receiving Peritoneal Dialysis

Patients with advanced malignancies commonly experience hypercalcemia. Hypercalcemia is resistant to medical management and may require hemodialysis for immediate correction. However, according to **Catherine Vatsis, MD,** and colleagues at the University of Texas MD Anderson Cancer Center, Houston, Texas, and Baylor College of Medicine, Houston, Texas, management of hypercalcemia in patients receiving peritoneal dialysis is more challenging.

During a poster session at the NKF Spring Clinical Meetings 2023, the researchers presented a case report of a patient with end-stage renal disease (ESRD) receiving peritoneal dialysis who presented to the emergency department (ED) with hypercalcemia. The poster was titled *Hypercalcemia in Peritoneal Dialysis Patients; Management Quandaries.*

The patient was a Black male, 79 years of age, with a history of ESRD, and receiving peritoneal dialysis for 3 months. He had been diagnosed with follicular lymphoma grade 2 of extranodal sites and chronic hepatitis B. He presented to the ED with altered mental state (AMS) and was hypercalcemic at 13.8 mg/dL.

He had not missed any of his peritoneal dialysis treatments as per medical records and family reports. He was admitted for workup and treatment of hypercalcemia and AMS. On admission, parathyroid hormone (PTH) was low at 8.1 pg/ml and PTH-related peptide was 1.3 pmol/L, suggesting a non-PTH driver of hypercalcemia. Serum protein electrophoresis test was normal, as was 25 OH vitamin D. However, 1,25 (OH)2 vitamin D level was elevated at 111 ng/mL.

Treatment with intravenous calcitonin was initiated, followed by denosumab and then prednisone for the hypercalcemia. His peritoneal dialysis bath was changed to low calcium solution. Despite treatment, he remained severely hypercalcemic and was transitioned to hemodialysis at day 7 following admission.

The researchers noted that because patients with ESRD receiving peritoneal dialysis typically have adynamic bone disease, hypercalcemia is relatively uncommon in that population. When a patient presents with hypercalcemia, secondary causes such as malignancy need to be identified. Management of patients on peritoneal dialysis diagnosed with hypercalcemia is challenging due to the absence of zero calcium peritoneal solutions and few available data on the effect of peritoneal dialysis on clearance of commonly used drugs for hypercalcemia.

"Hypercalcemia in ESRD patients on peritoneal dialysis is difficult to manage and may need urgent transition to intermittent hemodialysis," the researchers added.

Source: Vatsis C, Ajaz A, Ward K, Fareedy S, Workeneh B, Mandayam S. Hypercalcemia in peritoneal dialysis patient: management quandaries. Poster #191. Abstract of a poster presented at the National Kidney Foundation Spring Clinical Meetings 2023; April 11-15, 2023; Austin, Texas.

Managing Paxlovid-Induced Toxicity in Kidney Transplant Recipients

Kidney transplant recipients with COVID-19 infection have significant risk of severe disease. Nirmatrelvir/ritonavir (Paxlovid; NMV/r) has US Food and Drug Administration Emergency Use Authorization to treat high-risk patients with mild-to-moderate COVID-19 infection. NMV/r has a significant drug-drug interaction with calcineurin inhibitors (CNIs), according to researchers.

During a poster session at the NKF Spring Clinical Meetings 2023, **Lillia Harris, MD,** and colleagues at the University of Mississippi Medical Center, Jackson, Mississippi, described two cases of NMV/r-induced tacrolimus toxicity in kidney transplant recipients. The poster was titled *Paxlovid-Induced Tacrolimus Toxicity in Kidney Transplant Recipients.*

The two kidney transplant recipients were receiving maintenance immunosuppression (tacrolimus, mycophenolate mofetil, prednisone). They were admitted to the medical center with respiratory failure due to COVID-19 and acute kidney injury.

Within a week prior to admission, both patients tested positive for COVID-19 and received NMV/r with no adjustment of tacrolimus doses. At admission, tacrolimus levels were >60 ng/mL and remained >60 ng/mL despite holding tacrolimus. To enhance tacrolimus hepatic metabolism, oral phenytoin 100 mg twice daily was started. The day following administration of phenytoin, tacrolimus levels began to decrease. Both patients recovered and kidney function improved.

Because NMV/r is an inhibitor of CPY23 enzymes, it predisposes transplant recipients on CNIs to serious toxicities. At present, there are no guidelines regarding CNI management when prescribing NMV/r in this patient population; however, it is advised to significantly reduce CNI dose or completely stop use of CNIs while on NMV/r. Tacrolimus level should be monitored frequently as well.

"Paxlovid use in kidney transplant recipients on CNIs or mTOR [mammalian target of rapamycin] inhibitors posed a high risk of serious side effects and toxicities. Phenytoin can be used to manage CNI toxicity," the researchers stated.

Source: Harris L, Vaitla P, Atari M. Paxlovid-induced tacrolimus toxicity in kidney transplant recipients. Poster #75. Abstract of a poster presented at the National Kidney Foundation Spring Clinical Meetings 2023; April 11-15, 2023; Austin, Texas.

Pegloticase in Kidney Transplant Recipients With Gout

Kidney transplant recipients with gout and hyperuricemia face increased risks for adverse outcomes. Results of the PROTECT study demonstrated that pegloticase lowered serum urate in 89% of kidney transplant recipients with uncontrolled gout.

During a poster session at the NKF Spring Clinical Meetings 2023, **Nicola Dalbeth, MBChB, MD,** and colleagues reported associated changes in monosodium urate deposition volume (V_{msu}) as seen on dual-energy computed tomography (DECT). The poster was titled *Monosodium Urate Crystal Depletion in Renal Transplant Recipients Treated With Pegloticase: PROTECT Serial Dual-Energy Computed Tomography Findings.*

Inclusion criteria were uncontrolled gout (serum urate, ≥7 mg/dL; oral urate-lowering therapy refractory/intolerant; and ≥2 flares/year, ≥1 tophi, or chronic gouty arthritis), kidney transplant >1 year prior, graft estimated glomerular filtration rate (eGFR) ≥15 mL/min/1.73 m^2, and stable immunosuppression. All patients received ≤24 weeks of pegloticase (8 mg biweekly; serum urate response, <6 mg/dL for ≥80% of month 6).

DECT imaging was measured with standard protocols at screening (Scr). V_{msu} was measured at weeks 14 and 24 with default postprocessing settings. Joints with Scr and week 24 images and Scr V_{msu} ≥0.5 cm^3 were included. The V_{msu} criterion reduced the effects of DECT artifact.

Eight patients underwent imaging. All eght were male, mean age was 52.3 years, mean time since kidney transplant was 18.7 years, mean eGFR was 45.6 mL/min/1.73 m^2, and mean serum urate was 10.4 mg/dL. Six of the eight received 24 weeks of pegloticase and were serum urate responders (week 24 serum urate, 0.5 mg/dL). Two patients discontinued the study due to COVID-19.

Five imaged regions of four responders met inclusion criteria for the current analysis. In all joints, V_{msu} rapidly and progressively decreased (≥96% reduction at week 24; mean, -98.9).

"In this kidney transplant recipient population, sustained profound serum urate lowering was associated with a rapid, marked decrease in V_{msu} on DECT," the researchers concluded.

Source: Dalbeth N, Abdellatif A, Botson J, et al. Monosodium urate crystal depletion in renal transplant recipients treated with pegloticase: PROTECT serial dual-energy computed tomography findings. Poster #430. Abstract of a poster presented at the National Kidney Foundation Spring Clinical Meetings; April 11-15, 2023; Austin, Texas.

Urinary Biomarkers of Renal Injury in Patients With Diabetic Nephropathy

Previous studies have examined the association of hyperuricemia and chronic kidney disease (CKD). However, according to **Brad Marder, MD,** and colleagues at NephroNet Clinical Trials Consortium, Atlanta, Georgia, it has been difficult to identify patients at risk of uric acid nephropathy and progressive CKD. Earlier studies have demonstrated that patients with gout have elevated urinary levels of kidney injury molecule-1 (KIM-1) and monocyte chemotactic protein-1 (MCP-1), but the association between those elevated levels and proteinuria or decline in estimated glomerular filtration rate (eGFR) is unclear.

The researchers have suggested using KIM-1 and MCP-1 as biomarkers to identify patients at risk for uric acid nephropathy and progressive CKD. They conducted a prospective study of KIM-1 and MCP-1 in 25 patients with CKD stage 3b from type 2 diabetic nephropathy mellitus. Results were reported during a poster session at the NKF Spring Clinical Meetings 2023 in a poster titled *Comparative Levels of Urinary Biomarkers of Renal Injury and Inflammation Among Patients With Diabetic Nephropathy With or Without Hyperuricemia.*

The 25 patients were categorized as (1) patients with normal controls (uric acid <5.0 mg/dL; n=10) and (2) patients with hyperuricemia (uric acid >7.0 mg/dL; n=14). Urine samples for KIM-1 and MCP-12 were obtained from first morning urine voids separated by 3 weeks and stored at -80 degrees C until batch assayed.

Of the 10 patients in the control group, 73% were White, 55% were male, median age was 74 years, and duration of CKD was 4.5 years. Among the 14 patients in the hyperuricemia group, 71% were White, 50% were male, median age was 67 years, and duration of CKD was 3.7 years.

In the control group, baseline eGFR was 43 mL/min/1.73 m^2, and baseline serum uric acid level was 5.1 mg/dL. Annualized change in eGFR was +0.93 mL/min/1.73 m^2 per year, and current serum acid level was 5.7 mg/dL. In the hyperuricemia group, baseline eGFR was 45.6 mL/min/1.73 m^2, and baseline serum uric acid level was 9.07 mg/dL. Annualized decline in eGFR was -3.31 mL/min/1.73 m^2 per year, and current serum uric acid was 7.73 mg/dL.

"We demonstrated that urinary elevations in both MCP-1 and KIM-1 are associated with higher serum uric acid and urinary protein with a trend toward accelerated decline in eGFR," the researchers said. "Use of the biomarkers may help to identify subpopulations of hyperuricemic patients that would benefit from reductions in serum uric acid."

Source: Alex R, Press E, Marder B, Paxton B, Tumlin J. Comparative levels of urinary biomarkers of renal injury and inflammation among patients with diabetic nephropathy with or without hyperuricemia. Poster #277. Abstract of a poster presented at the National Kidney Foundation Spring Clinical Meetings 2023; April 11-15, 2023; Austin, Texas. The study was supported by Horizon Pharmaceuticals as an independent grant to the NephroNet Clinical Trials Consortium.

Red Blood Cell Transfusions in Patients With CKD and Anemia

According to Jake Hunnicutt, PhD, and colleagues, there are few data on the use of red blood cell transfusion among patients with anemia and nondialysis dependent chronic kidney disease (CKD) in the United States. Data on how the rates of red blood cell transfusion vary by hemoglobin level are also limited.

During a poster session at the NKF Spring Clinical Meetings 2023, the researchers presented data on the rate of red blood cell transfusions and associated complications from 2017 to 2019. The poster was titled *Red Blood Cell (RBC) Transfusion Use Varies by Baseline Hemoglobin (Hb) and Is Associated With Posttransfusion Hyperkalemia and Hospitalization Within 30 Days in US Patients With Stage 3-5 CKD and Anemia.*

The retrospective cohort study utilized Optum's deidentified Integrated Claims-Clinical dataset. Inclusion criteria were hemoglobin measure (index date), prior evidence of stage 3-5 CKD, and anemia (defined as treatment for anemia or baseline hemoglobin <12 g/dL for women or <13 g/dL for men). Analyses were stratified by insurance type (commercial or Medicare Advantage [MA]).

Associations between baseline hemoglobin and red blood cell transfusion events within 6 months were quantified using estimated adjusted rate ratios (aRR) and 95% CIs. Claims data were used to identify episodes of hyperkalemia and all-cause hospitalization with 30 days of initial red blood cell transfusion.

The study cohort included 10,712 patients with commercial insurance (54% female, mean age 58.8 years) and 64,554 patients with MA (59% female, mean age 77.8 years). During the 1-year baseline period, only 2.8% of commercially insured patients and 2.1% of the MA-insured patients received intravenous iron. During that period, only 1.2% of the commercial insurance group and 1.2% of the MA group were treated with erythropoiesis-stimulating agents (ESAs).

During follow-up, there was an association between lower baseline hemoglobin and an increased rate of red blood cell transfusion events. Within 30 days of the initial red blood cell transfusion, hyperkalemia was observed in 12.7% of patients in the commercial insurance group and in 12.1% of those in the MA insurance group. During that same period, 35.8% of those in the commercial insurance group and 46.1% of those in the MA group had one or more hospitalizations.

In summary, the researchers said, "Red blood cell transfusion was more common in patients with nondialysis-dependent stage 3-5 CKD and anemia between 2017 and 2019, and more frequent in patients with low baseline hemoglobin. Baseline use of iron and ESAs was low. Hyperkalemia and hospitalizations were common following a transfusion."

Source: Red blood cell (RBC) transfusion use varies by baseline hemoglobin (Hb) and is associated with posttransfusion hyperkalemia and hospitalization within 30 days in US patients with stage 3-5 CKD and anemia. Poster #182. Abstract of a poster presented at the National Kidney Foundation Spring Clinical Meetings 2023; April 11-15, 2023; Austin, Texas. Funding for the study was provided by GSK (Study 218794).

Investigative Autologous Cell Trials in DKD

In Mississippi, a state with a disproportionately high prevalence of diabetic kidney disease (DKD), less than 10% of patients at high risk receive adequate testing. DKD is associated with adverse outcomes and costs and creates a significant burden on the state's health care system.

During a poster session at the NKF Spring Clinical Meetings 2023, **Davis Rippee** and colleagues reported on two novel investigative autologous cell trials underway in Mississippi that have the potential to improve renal function and delay initiation of dialysis. The poster was titled *Novel Renal Autologous Cell Therapy (REACT) for Chronic Kidney Disease With Diabetes (DKD): Investigative Trial Experience in Mississippi.*

The two US Food and Drug Administration (FDA)-approved phase 2 trials are being conducted in Tupelo with Nephrology & Hypertension Associates, Ltd., and North Mississippi Medical Center. Participants with DKD and estimated glomerular filtration rate (eGFR) 20 to 50 mL/min/1.73 m^2 receive outpatient percutaneous kidney biopsy. The biopsy undergoes *ex vivo* culture expansion of selected renal cells that are formulated, returned to North Mississippi Medical Center, and reinjected into the kidney cortex with computed tomography guidance.

In the first trial (NCT02836574), 83 patients were randomized to receive either two injections 6 months apart into the biopsied kidney or standard of care for 12 months followed by two REACT injections in the same protocol. In the second trial (NCT05018416), 50 patients will be randomized into two treatment cohorts. Patients in cohort 1 will receive two REACT injections 3 months apart, one in each kidney. Patients in cohort 2 will receive one injection and following attainment of a predefined trigger (decline in eGFR of ≥20% or >30% decrease in urine albumin-creatinine ratio >30 mg/g) will receive a second injection in the contralateral kidney.

The follow-up period for both trials is 18 months post-injections. Outcomes of interest include safety and change in kidney function as measured by eGFR.

Preliminary evidence has demonstrated preservation of kidney function as measured by eGFR compared with baseline (P=.015) and favorable impact on albuminuria. The potential to delay time to kidney failure supported FDA and European Medicines Agency regulatory allowance of two global phase 3 REACT trials.

"Cell-based therapies have the potential to effect nephron structure and function by preserving, stabilizing, or improving DKD progression and comorbidities. Current phase 2/3 trials will determine efficacy, safety, renal dosing, and time to treatment with bilateral kidney injections," the researchers said.

Source: Rippee D, Wooldridge T, Dossabhoy N, et al. Novel renal autologous cell therapy (REACT) for chronic kidney disease with diabetes (DKD): investigative trial experience in Mississippi. Poster #247. Abstract of a poster presented at the National Kidney Foundation Spring Clinical Meetings 2023; April 11-15, 2023; Austin Texas.

Four-Year Liver Safety Data From the Tolvaptan REMS

Patients in the United States with autosomal dominant polycystic kidney disease (ADPKD) treated with tolvaptan in clinical practice must enroll in a risk evaluation and mitigation strategy (REMS) that includes education of health care providers and patients regarding the risk for liver injury, the need for regular liver chemistry monitoring, and the reporting of adverse events suggesting serious and potentially fatal liver injury.

An interim 3-year analysis of REMS liver safety data has been published previously. During a poster session at the NKF Spring Clinical Meetings 2023, **Michael Lioudis, MD,** and colleagues provided an updated analysis of 4 years of REMS data. The poster was titled *Post-Marketing Liver Safety Data From 4 Years of the Tolvaptan Risk Evaluation and Mitigation Strategy (REMS) in the Treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD).*

Participating health care providers are required to report adverse events suggestive of serious and potentially fatal liver failure to the manufacturer's Global Pharmacovigilance database. In compliance with FDA guidance on evaluating potential drug-induced liver injury, confirmation is obtained using provided evidence, including laboratory data and trends over time, diagnostic tests, symptoms, medical history, event time course, confounding risk factors, and concomitant medications. The current analysis included data from implementation of the REMS (May 14, 2018) to February 24, 2022.

Of the 8764 patients in the tolvaptan-naive safety sample, four were confirmed with serious and potentially fatal liver injury. All four patients promptly discontinued tolvaptan and experienced normalization of liver enzyme. As previously reported, they were all detected prior to the 14-month REMS interim assessment. There were no additional cases following the 2-year data cut-off.

In the entirety of the 4-year reporting period, there were no liver transplants or fatalities attributed to liver injury related to tolvaptan use. Ongoing follow-up is continuing to determine whether three events in year 4 (2/24/21-2/23/22) can be confirmed as serious and potentially fatal. The incidence of possible severe drug-induced liver injury was 0.78% (n=69/8764). The incidence continues to be lower in the REMS than in clinical trials (5.5%; n=151/2743).

In summary, the authors said, "Regular liver enzyme monitoring as specified in the REMS enables prompt detection of liver abnormalities and appropriate action to reduce risk of severe outcomes in the real world."

Source: Lioudis M, Nunna S, George V, Kuman R, Fernandes AW. Post-marketing liver safety data from 4 years of the tolvaptan risk evaluation and mitigation strategy (REMS) in the treatment of autosomal dominant polycystic kidney disease (ADPKD). Poster #350. Abstract of a poster presented at the National Kidney Foundation Spring Clinical Meetings 2023; April 11-15, 2023; Austin, Texas. Funding for the analysis was provided by Otsuka Pharmaceutical Development & Commercialization, Inc.

Costs of SZC Plus RAASi Therapy in Hyperkalemia

During a poster session at the NKF Spring Clinical Meetings 2023, **Jamie P. Dwyer, MD,** and colleagues reported results of a real-world study designed to examine the impact of sodium zirconium cyclosilicate (SZCV) therapy on 3-month medical costs in patients receiving renin-angiotensin-aldosterone system inhibitors (RAASi) prior to a diagnosis of hyperkalemia or dispensed SZC fill. The poster was titled *Impact of Sodium Zirconium Cyclosilicate Plus Renin-Angiotensin-Aldosterone System Inhibitor Therapy on Short-term Medical Costs in Hyperkalemia: OPTIMIZE II Study.*

A large US commercial claims database was used to retrospectively identify patients in the OPTIMIZE II study ≥18 years of age who were dispensed SZC ≥60-day supply and continued RAASi between July 2019 and December 2021. Eligible patients had continuous insurance coverage 6 months before (baseline) and 3 months after (follow-up) the index SZC fill.

Eligible patients (SZC cohort) were 1:1 exact and propensity-score matched on baseline variables with patients who did not receive SZC and discontinued RAASi following diagnosis of hyperkalemia (non-SZC cohort). The primary outcome of interest was medical costs related to hyperkalemia (any setting and diagnosis position) to payers over 3 months. The researchers also analyzed all-cause medical and pharmacy costs.

Each cohort included 467 matched patients. Mean hyperkalemia-related and all-cause medical costs were reduced by $2216 ($P$=.01) and $6102 ($P$<.001) per patient, respectively, in the SZC cohort versus the non-SZC cohort. There were also significant reductions in hyperkalemia-related and all-cause inpatient costs and all-cause emergency department costs in the SZC cohort versus the non-SZC cohort. In the SCZ cohort, the reduction in all-cause medical cost offset an increase in all-cause pharmacy cost (mean increase, $3118 per patient; P<.001).

In conclusion, the authors said, "SZC with continued RAASi therapy was associated with reduced hyperkalemia-related and all-cause medical costs compared with no SZC therapy and RAASi discontinuation after hyperkalemia diagnosis. This suggests potential medical cost savings by adding SZC to maintain RAASi."

Source: Dwyer JP, Agiro A, Desai P, Oluwatosin Y. Impact of sodium zirconium cyclosilicate plus renin-angiotensin-aldosterone system inhibitor therapy on short-term medical costs in hyperkalemia: OPTIMIZE II study. Poster #284. Abstract of a poster presented at the National Kidney Foundation Spring Clinical Meetings 2023; April 11-15, 2023; Austin, Texas. Support for the analysis was provided by AstraZeneca.

Awards and Honors

Health care professionals who have made significant contributions to the field of kidney disease were honored at the **National Kidney Foundation 2023 Spring Clinical Meetings**.

Susan Hedayati, MD, MHSc

The *Shaul G. Massry Distinguished Lecture* award was presented to **Susan Hedayati, MD, MHSc,** for her discoveries in kidney disease. Dr. Hedayati is the associate vice-chair for research in the Department of Internal Medicine, director of clinical and translational research in nephrology, and codirector of the O'Brien Kidney Clinical and Translational Core at the University of Texas Southwestern Medical Center.

Melanie Hoenig, MD

The *Donald W. Seldin Award* was established to recognize excellence in clinical nephrology. The recipient for 2023 is **Melanie Hoenig, MD.** Dr. Hoenig is a nephrologist at Beth Israel Deaconess Medical Center and associate professor at Harvard Medical School. Her clinical interests are kidney disease in the context of HIV and the transition to adult care for young people with kidney disease.

Cynthia Delgado, MD

The winner of the 2023 *Garabed Eknoyan Award*, given in recognition of an individual whose work promotes the mission of NKF in making lives better for people with kidney disease, is **Cynthia Delgado, MD.** Dr. Delgado is professor of medicine at the University of California, San Francisco. She is the associate chief of nephrology for clinical operations and the director of the dialysis program for the San Francisco Veterans Affairs Healthcare System.

Alfred K. Cheung, MD

The *David M. Hume Memorial Award* was created in memory of one of NKF's most distinguished members and is the highest honor given by the Foundation to a scientist-clinician in the field of kidney and urologic diseases. The 2023 recipient is **Alfred K. Cheung, MD.** Dr. Cheung is the Dialysis Research Foundation Presidential Endowed Chair and professor of internal medicine, chief of the Division of Nephrology & Hypertension, and vice chair for research in the Department of Internal Medicine at the University of Utah. His research focuses on chronic kidney disease, hemodialysis, vascular access, and hypertension.

Rajnish Mehrota, MD, MS

The *J. Michael Lazarus Award* recognizes individuals whose research has yielded novel insights related to renal replacement therapy. The 2023 recipient is **Rajnish Mehrota, MD, MS,** the Belding H. Scribner Endowed Chair in Medicine and the head of the Division of Nephrology in the Department of Medicine at the University of Washington School of Medicine, and chair of the Board of Trustees for Northwest Kidney Centers. He is a clinical and research expert in dialysis modalities and has been a strong advocate for home modalities, particularly peritoneal dialysis.

Lois Hill, MS, RDN, LD, LDE

The recipient of the 2023 *Joel D. Kopple Award* for work in the field of renal nutrition is **Lois Hill, MS, RDN, LD, LDE.** She is in private practice in Lexington, Kentucky, with a focus on nutrition counseling for patients with chronic kidney disease (CKD). She has worked in clinical practice with patients with stage 1-5 CKD as well as kidney transplant recipients, and has participated in research in nutrition in CKD.

Ana Ricardo, MD

Ana Ricardo, MD, is the recipient of the 2023 *Medical Advisory Board Distinguished Service Award.* The award is given to highlight community service and activities that promote NKF's mission on a local level. Dr. Ricardo is a member of the NKF of Illinois Professional Advisory Board Executive Committee. Her research focuses on health disparities and health behaviors in CKD. She has led clinical research studies evaluating racial and ethnic, as well as sex-related differences in CKD progression.

Jeanetta Wammack, RN, CDN

The Carol Mattix Award was created by the Council of Nephrology Nurses and Technicians to honor Carol Mattix who was a home dialysis training nurse whose tireless work improved the lives of kidney patients. The recipient for 2023 is **Jeanetta Wammack, RN, CDN,** a peritoneal dialysis nurse at Arkansas Children's Hospital, Little Rock. She has spent 24 of her 29 years of nursing working in the dialysis field, and has worked in nearly every facet of dialysis.

Tanjala S. Purnell, PhD, MPH, FASN

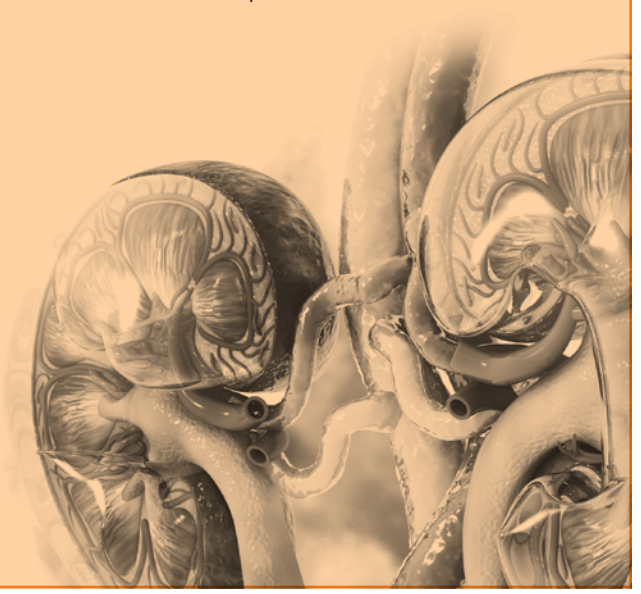
Tanjala S. Purnell, PhD, MPH, FASN, is the recipient of the 2023 *Excellence in Kidney Transplantation Award.* The award recognizes research that has contributed novel insights to improved access to kidney transplantation. Dr. Purnell is an associate professor of epidemiology and surgery at Johns Hopkins University, where she serves as the founding director of the BOLD Health Equity Initiative, director of education for the Brancati Center for the Advancement of Community Care, and executive director of the Health Freedom Path to Wellness program.

Maria Elena Grijalva

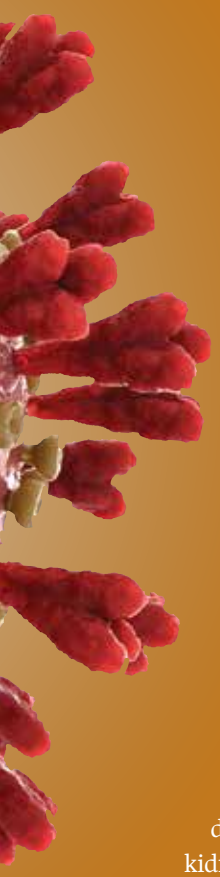
The 2023 *Celeste Castillo Lee Patient Engagement Award* was presented to **Maria Elena Grijalva,** a kidney patient advocate since receiving a kidney transplant 36 years ago. She devotes her efforts to educating Native American people and farmworkers in agricultural communities in California, and raising awareness about kidney health and kidney disease among high-risk populations.

Tom Duvall, MBA

The 2023 *Public Service Award* was presented to **Tom Duvall, MBA,** director, Centers for Medicare & Medicaid (CMS) Division of Special Populations and Projects at the CMS Innovation Center. He works in the Seamless Care Models Group and oversees multiple payment model tests focused on improving care for beneficiaries with kidney disease, as well as two payment models focused on rural hospitals.



Acute Kidney Injury in Patients With COVID-19, Influenza, and RSV



A significant portion of patients with COVID-19 infection experience acute kidney injury (AKI); rates of AKI among patients admitted to the intensive care unit (ICU) are very high. Reported rates among hospitalized patients range from 15% to 40%, and rates in patients admitted to the ICU exceed 50%. Approximately 5% of patients hospitalized with COVID-19 required renal replacement therapy (RRT); among patients in the ICU, up to 15% required RRT.

Mechanisms associated with AKI in COVID-19 include direct viral penetration of renal cells through the angiotensin converting enzyme 2 receptor. Renal failure can also result from indirect damage by the aberrant inflammatory response characteristic of COVID-19.

A severe inflammatory response to viral infection is not unique to SARS-CoV-2. AKI is also associated with other common respiratory viruses such as influenza and respiratory syncytial virus (RSV). **Eden Shusterman, MD,** and colleagues in Israel conducted a retrospective observational study in a tertiary medical center to compare the rate, risk factors, and prognostic value of AKI among those viruses. Results were reported online in the *Journal of Nephrology* [doi.org/10.1007/s40620-023-01591-2].

The cohort included three groups: (1) 2593 patients ≥18 years of age admitted to the Tel Aviv Sourasky Medical Center (TASMC) with a confirmed diagnosis of SARS-CoV-2 infection from March 2020 until November 2021; (2) 2041 patients with a confirmed diagnosis of influenza infection (A and B) admitted to TASMC between 2010 and 2020; and (3) 429 patients with a confirmed diagnosis of RSV admitted to TASMC from 2010 to 2020. Patients undergoing chronic RRT were excluded, as were those for whom blood tests were not available.

Using patient chart reviews, the researchers obtained background data on sex, age, comorbidities, diagnoses known as risk factors for AKI in COVID-19 (hypertension, diabetes mellitus, multiple myeloma, heart failure, chronic kidney disease [CKD], and chronic use of specific medications [angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or proven risk factors for COVID-19-related AKI such as diuretics]). Other data of interest were vital signs; laboratory data on blood count, blood chemistry, urine analysis, and blood gases; and general clinical outcomes (length of hospitalization, need for mechanical ventilation, and morbidity).

In general, patients in the RSV group were older and had more comorbidities compared with the other two groups. In the COVID-19 group, hypertension and diabetes mellitus were least common in contrast to the RSV group, where hypertension and diabetes mellitus were most common ($P<.001$ for hypertension and $P<.05$ for diabetes mellitus).

Patients with COVID-19 had the worst outcomes, with higher rates of death (18% vs 7% vs 13% for COVID-19, influenza, and RSV, respectively; $P<.001$) and higher rates of need for mechanical ventilation (13% vs 6% vs 8% for COVID-19, influenza, and RSV, respectively; $P<.001$). In the COVID-19 and influenza groups, those with AKI on admission had significantly longer lengths of stay.

Rates of AKI were measured at admission, at 48 hours, and within 7 days. Compared with the groups with influenza or RSV, those with COVID-19 had the lowest rates of AKI at all time points: at admission, 7.33 vs <8.04 vs <11.19 for COVID-19, influenza, and RSV, respectively ($P=.03$); after 48 hours, 2.97 vs <5.14 vs <8.16 for COVID-19, influenza, and RSV, respectively ($P<.001$); and within 7 days, 11.76 vs <13.28 vs <17.95 for COVID-19, influenza, and RSV, respectively ($P=.002$). No virus was an independent risk factor for AKI within 7 days or a risk factor for stage 3 AKI. Temporal patterns were similar in the three groups regarding creatinine dynamics, which was skewed to the first 48 hours of admission, with the highest proportion of patients reaching their maximal creatinine within 48 hours.

Across the three groups, CKD, high levels of phosphate, proteinuria, and blood urea nitrogen (BUN) were independent risk factors for developing AKI, as was elevated neutrophil to lymphocyte ratio within 48 hours of admission. For all three viruses, CKD, proteinuria, and high levels of phosphate and BUN on admission were predictors of stage 3 AKI. Higher phosphate levels on admission were a strong risk factor for stage 3 AKI. High ferritin levels and low oxygen saturation were independent risk factors for severe AKI in the COVID-19 group only.

In all three groups, there was a strong and independent association between development of AKI within the first 7 days of admission and the risk for adverse outcomes (death within 30 days or the need for mechanical ventilation). There was also a strong and independent association between developing stage 3 AKI within the first 7 days of AKI and the risk of adverse outcomes.

AKI on admission was a predictor of adverse outcomes only in the COVID-19 and influenza groups. AKI within the first 48 hours was a significant risk factor for adverse outcomes in all three groups. Patients in the COVID-19 and influenza groups whose creatinine continued or began to rise after more than 48 hours from admission had an increased risk for adverse outcomes.

The authors cited some limitations to the study, including the retrospective design and the asymmetrical temporal formation of the three groups. During the early phase of the COVID-19 pandemic, patients with mild symptoms were referred to the emergency department, while hospitalized patients were screened for COVID-19, which may have resulted in selection bias.

In conclusion, the researchers said, "Our study compared the renal risk factors, the outcomes, and the prognostic factors in patients affected by three respiratory viruses. To our knowledge, this is the first large-scale study reporting on renal injury in hospitalized RSV patients. We found that, despite the growing evidence for COVID-19 tropism and direct kidney injury, the incidence of acute kidney injury is not higher than that observed with other viruses. COVID-19 is unique, however, in the prognostic value of inflammatory markers for predicting renal injury, which may pertain to the specific role of the aberrant immune response in kidney damage. We were further able to define the prognostic value of AKI at several time points on the overall outcome. In the near future, when influenza, COVID-19, and RSV may circulate simultaneously, our findings could provide a virus-specific evaluation, allowing clinicians to estimate the expected renal and overall outcomes." ■

TAKEAWAY POINTS

- Patients with COVID-19 admitted to the intensive care unit have high rates of developing acute kidney injury (AKI).
- Researchers in Israel compared rates, risk factors, and outcomes of AKI in patients with COVID-19 with those in patients with influenza (A and B) and patients with respiratory syncytial virus (RSV).
- The incidence of AKI was lower in patients with COVID-19 compared with patients with influenza or RSV. In all three viruses, AKI was a prognostic marker for adverse outcomes.

Differences in Estimated GFR by Creatinine Versus Cystatin C and Heart Failure Risk

Patients with chronic kidney disease (CKD) face increased risk of developing heart failure. There is a strong and independent association between lower estimated glomerular filtration rate (eGFR) and risk of heart failure events. There are variations in eGFR among individual patients depending on whether creatinine or cystatin C is used for estimation of GFR. Cystatin C had been shown to have stronger and more linear associations with incident heart failure compared with creatinine; however, creatinine-based eGFR ($eGFR_{cr}$) is more widely used in clinical practice than cystatin C-based eGFR ($eGFR_{cys}$).

Previous studies with population-based cohorts or clinical trials have found associations of the difference in GFR estimates ($eGFR_{diff}$, defined as $eGFR_{cys}$ minus $eGFR_{cr}$). According to **Debbie C. Chen, MD,** and colleagues, the associations of $eGFR_{diff}$ with hospitalizations for heart failure have not been examined in a cohort of participants with established CKD. There are also only few available data on the clinical interpretation of changes in $eGFR_{diff}$ over time.

Dr. Chen et al conducted a prospective cohort study to answer three questions: (1) Among individuals without prevalent heart failure at baseline, is baseline $eGFR_{diff}$ independently associated with incident heart failure hospitalization? (2) Does the inclusion of time-updated measures yield stronger associations between $eGFR_{diff}$ and incident heart failure? (3) Is widening or narrowing of $eGFR_{diff}$ over time independently associated with incident heart failure? Results were reported in the *American Journal of Kidney Diseases* [2022;80(6):762-771].

The study cohort included adults with CKD and without prevalent heart failure who enrolled in the CRIC (Chronic Renal Insufficiency Cohort) study. The study exposure was the difference in GFR estimates ($eGFR_{diff}$ [$eGFR_{cys}$ minus $eGFR_{cr}$]). The outcome of interest was incident heart failure hospitalization. The associations of baseline, time-updated, and slope of $eGFR_{diff}$ with incident heart failure were investigated using Fine-Gray proportional subhazards regression.

A total of 4512 CRIC study participants were included in the analysis. Of those,

44% (n=1981) were female, 42% (n=1906) were non-Hispanic Black, and 11% (n=447) were Hispanic. Mean age was 59.4 years, $eGFR_{cys}$ was 55 mL/min/1.73 m^2 , and mean $eGFR_{cr}$ was 49 mL/min/1.73 m^2. Baseline $eGFR_{diff}$ ranged from –52 to 65 mL/min/1.73 m^2.

A total of 2977 patients had a midrange baseline $eGFR_{diff}$ (eGFRcys similar to $eGFR_{cr}$); 340 had a negative baseline $eGFR_{diff}$ ($eGFR_{cys}$ lower than $eGFR_{cr}$); and 1195 had a positive baseline $eGFR_{diff}$ ($eGFR_{cys}$ higher than $eGFR_{cr}$). Those in the negative $eGFR_{diff}$ group were generally older and had the highest prevalence of diabetes and cardiovascular disease compared with the other two groups. Those in the $eGFR_{diff}$ positive group were younger and had lower prevalence of baseline comorbidities and medication use.

Twelve percent (n=532) of the study participants developed incident heart failure, with median time to incident heart failure hospitalization of 3.5 years. Following adjustment for demographics and eGFR, there was an association between each 15-mL/min/1.73 m^2 lower baseline $eGFR_{diff}$ and a 56% higher risk of incident heart failure. After additional multivariable adjustment, the association was attenuated to 20%. Participants with negative $eGFR_{diff}$ had the highest crude rate of incident heart failure, and those with positive $eGFR_{diff}$ had the lowest incidence of heart failure. Compared with the midrange $eGFR_{diff}$ group, the positive and

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negative $eGFR_{diff}$ groups were not statistically significantly associated with multivariable-adjusted risk of incident heart failure.

Following multivariable adjustments accounting for time-updated $eGFR_{diff}$ and covariates, there was an association between each 15 mL/min/1.73 m^2 lower baseline $eGFR_{diff}$ and 36% higher risk of incident heart failure. Compared with the group with midrange $eGFR_{diff}$, the adjusted risk of incident heart failure was higher among participants in the group with negative $eGFR_{diff}$ (subdistribution hazard ratio [HR], 1.99; 95% CI, 1.39-2.86), and those in the positive $eGFR_{diff}$ group had a lower adjusted risk of incident heart failure (subdistribution HR, 0.67; 95% CI, 0.49-0.91). There was modest attenuation with further adjustment for markers of nutritional status and inflammation.

Slopes of $eGFR_{diff}$ were derived using a median of four annual $eGFR_{diff}$ values. The mean annual change in $eGFR_{diff}$ was –0.4 mL/min/1.73 m^2. Following adjustment for baseline $eGFR_{diff}$, in multivariable models including adjustment for baseline $eGFR_{diff}$, each 1-SD lower $eGFR_{diff}$ slope was associated with 37% higher risk of incident heart failure. Participants with faster declines in $eGFR_{cys}$ relative to $eGFR_{cr}$ had higher risk of incident heart failure (HR, 1.49; 95% CI, 1.19-1.85) compared with those in whom $eGFR_{cys}$ and $eGFR_{cr}$ declined in parallel.

The researchers cited some limitations to the study findings, including entry into the CRIC study being determined by $eGFR_{cr}$, the use of the absolute rather than relative difference between $eGFR_{cys}$ and $eGFR_{cr}$, not calibrating cystatin C measures to a traceable international standard, lack of sufficient data on ejection fraction at the time of hospitalization for heart failure, and using a joint model to obtain within-participant estimates of $eGFR_{diff}$ slope.

In summary, the authors said, "Our study showed that large differences between $eGFR_{cys}$ and $eGFR_{cr}$ convey important prognostic information regarding risk of incident heart failure hospitalization. During longitudinal follow-up, steeper declines in $eGFR_{cys}$ than $eGFR_{cr}$ portend higher risk of heart failure events. Thus, in patients with CKD, annual measures of serum creatinine and cystatin C and separate reporting of both $eGFR_{cys}$ and $eGFR_{cr}$ could optimize the assessment of heart failure risk." ■

TAKEAWAY POINTS

- Researchers reported results of a prospective cohort study designed to assess the clinical implications of differences in estimated glomerular filtration rate based on cystatin C ($eGFR_{cys}$) and eGFR based on creatinine ($eGFR_{cr}$) on the risk of heart failure in individuals with chronic kidney disease.
- The study cohort included participants in the CRIC (Chronic Renal Insufficiency Cohort) study, a multicenter, observational cohort study that enrolled 5499 adults from seven clinical centers in the United States.
- Among participants with large differences between $eGFR_{cys}$ and $eGFR_{cr}$, there was an increased risk of incident heart failure; diverging slopes between $eGFR_{cys}$ and $eGFR_{cr}$ over time were also independently associated with the risk of incident heart failure.

Health Care Utilization After Dialysis-Treated AKI in Children

Acute kidney injury (AKI) is a common complication among hospitalized children and neonates. In recent decades, the incidence of dialysis-treated AKI among hospitalized children has increased significantly. There are associations between pediatric AKI and increased hospital length of stay, mortality, and health care costs. Results of previous studies have demonstrated that the long-term risks of chronic kidney disease (CKD), hypertension, kidney failure, and death are higher in children with dialysis-treated AKI.

AKI is associated with postdischarge heath care utilization and costs in adults. There are limited data regarding long-term follow-up and health care utilization and costs in children. **Cal H. Robinson, MD,** and colleagues conducted a retrospective cohort study to evaluate health care utilization and physician follow-up patterns following dialysis-treated AKI in a pediatric population. Results were reported in the *American Journal of Kidney Diseases* [2023;81(1):79-89].

The study cohort included all children 0 to 18 years of age who were hospitalized in Ontario, Canada, between 1996 and 2017. Individuals were excluded if they were not residents of Ontario; had metabolic disorders or poisoning; and had received dialysis or kidney transplant prior to admission, a kidney transplant by 104 days following discharge, or were receiving dialysis 76 to 104 days from dialysis start date.

The study exposure was episodes of dialysis-treated AKI, identified using validated health administrative codes. Survivors of AKI were matched to four hospitalized controls without dialysis-treated AKI by age, sex, and admission year. The primary outcome of interest was post-discharge hospitalizations, emergency department (ED) visits, and outpatient physician visits. Secondary outcomes included outpatient visits by physician type and composite health care costs.

Negative binomial regression models were used to determine the association between dialysis-treated AKI status and rehospitalizations, ED visits, and outpatient physician visits.

A total of 1688 hospitalized pediatric patients with dialysis-treated AKI were matched with 6752 patients hospitalized without dialysis-treated AKI between April 1996 and March 2017. Median age for the two groups was similar (5 years vs 5 years), as was sex distribution (45.9% female vs 45.9% female). As of the index hospitalization, 27.0% (n=455) of the dialysis-treated AKI survivors and 21.6% (n=1458) of the control group were <1 year of age.

At baseline, the prevalence of complex chronic disease was higher in the dialysis-treated AKI survivor group compared with the control group (29.5% vs 12.6%, respectively). Patients in the dialysis-treated AKI group were more frequently admitted to an academic children's hospital (77.2% vs 32.0% in controls) and more frequently admitted to the intensive care unit compared with controls (65.8% vs 8.8%, respectively). Among those in the dialysis group, 7.1% (n=111) had cardiac surgery prior to their index date, and 33.6% (n=568) underwent cardiac surgery during the index hospitalization. Baseline health care utilization was similar between the groups.

Duration of follow-up was similar in the two groups (median of 9.1 years in the dialysis recipients vs 9.8 years in the control group). During the analyzed follow-up years, kidney failure with replacement therapy (maintenance dialysis or kidney transplant) occurred in 44 dialysis recipients (2.6%) versus 10 in the control group (0.1%). De novo CKD occurred in 213 patients in the dialysis group (13.1%) compared with 113 patients in the control group (1.7%).

For all outcomes (rehospitalization, ED visits, and outpatient physician visits) and throughout the follow-up period, rates of health care utilization were higher in the dialysis-treated AKI survivor group than in the control group. Rates of health care utilization were higher within 1 year after the index date than in other follow-up periods.

During the first year of follow-up, rates of rehospitalization for dialysis-treated AKI survivors were twice that of the control group (879.3 vs 432.77 events per 1000 person-years, respectively).

In both groups, more than 90% visited a primary care provider by 1 year after the index date (92.2% in the dialysis group vs 90.9% in the control group). In the dialysis-treated AKI survivor group, only 18.6%, 24.6%, and 26.8% had a nephrology follow-up visit by 1, 5, and 10 years, respectively. Nephrologist follow-up within 1 year after the index date was less common in the dialysis-treated AKI survivors who underwent cardiac surgery than among those who did not undergo cardiac surgery (7.6% vs 24.2%, respectively).

Patients in the dialysis-treated AKI survivors group had a nephrology visit significantly sooner than those in the control group; the difference was greatest in the first year of follow-up. In adjusted regression analyses, exposure to dialysis-treated AKI was associated with an increased risk of rehospitalization (adjusted rate ratio [aRR], 1.46; 95% CI, 1.25-1.69; $P<.001$) and with increased risk of outpatient visits (aRR, 1.16; 95% CI, 1.09-1.23; $P=.01$). There was no increased risk of visits to the ED.

Composite health care costs among patients in the dialysis-treated AKI survivors group totaled $18 million Canadian dollars (CAD) within 1 year after the index date and $44 million CAD by 10 years. Median cost per person-year for dialysis recipients was three times that of patients in the control group in the first year ($2633.5 vs $881.0 per person-year). That relationship stayed consistent at the end of follow-up (median costs, $2549.1 per person-year for dialysis recipients and $887.8 per person-year for controls).

The researchers cited some limitations to the study findings, including the use of administrative database research that creates the possibility of miscoding of study exposure or outcomes, the possibility of residual confounding, and lack of data for health care costs before 2006 and for ED visits before 2001.

"In summary," the researchers said, "we found that dialysis-treated AKI survivors had higher long-term rehospitalization rates, outpatient visit rates, and health care costs but no difference in ED visits versus hospitalized controls. Nephrologist follow-up was infrequent after dialysis-treated AKI. The increasing incidence of dialysis-treated AKI places a significant burden on Ontario's health care system. Further research should evaluate the impact of dedicated post-AKI clinics and other tertiary prevention strategies on patient outcomes, including health care utilization." ■

TAKEAWAY POINTS

- Researchers reported results of a study designed to examine health care utilization and physician follow-up patterns following dialysis-treated acute kidney injury (AKI) in a pediatric population in Ontario, Canada.
- Compared with matched controls, dialysis-treated AKI survivors had higher rates of rehospitalization and emergency department visits during the analyzed follow-up periods (0-1, 0-5, and 0-10 years postdischarge).
- Health care costs were higher in patients in the dialysis-treated AKI survivor group compared with patients in the control group ($2633 vs $881 per person-year, respectively).

Transplant Rates and Outcomes in Adults With Intellectual and Developmental Disabilities

At present, the demand for donor organs is outpacing the supply, creating a need for transplant centers to prioritize which patients are put on the transplant waiting list. According to **Brittany N. Hand, PhD,** and colleagues, despite legislation such as the Americans With Disabilities Act, Rehabilitation Act, and the Affordable Care Act that prohibit discrimination against people with disabilities, individuals with intellectual and developmental disabilities (IDD) in need of a solid organ transplant continue to face such discrimination. Results of previous studies have suggested that 57% to 89% of surgeons consider moderate-to-profound intellectual disability a contraindication to transplant eligibility.

Reasons cited for excluding individuals with IDD from transplant wait lists include concerns regarding ability to follow post-transplant care, and increased risk for perioperative complications, mortality, or graft failure. However, recent data do not support this premise. Results of most pediatric studies have found similar transplant outcomes among children with and without IDD.

In light of an increasing national momentum to enact and enforce policies to improve equitable access to organ transplant for people with IDD, Dr. Hand et al conducted a retrospective cohort study designed to compare evaluation rates, kidney transplant rates, and transplant outcomes among adults with and without IDD. Results were reported online in *JAMA Surgery* [doi:10.1001/jamasurg.2022.7753].

The study included all Medicare inpatient and outpatient standard analytical files from 2013 through 2020. The study population included adults with end-stage kidney disease (ESKD) with and without co-occurring IDD, as well as a cohort of kidney transplant recipients with and without IDD.

A total of 413,655 adult Medicare beneficiaries with ESKD were identified. Using propensity-score matching, the cohorts of adults with and without IDD were balanced based on age, sex, race, follow-up duration, and Charlson Comorbidity Index. Data analysis occurred between June 2, 2022, and August 1, 2022.

The propensity score-matched cohort of patients with ESKD included 10,692 adults with IDD and 10,692 adults without IDD. Median age was 55 years and approximately 39% were male. The most common IDD diagnosis was other/unspecified intellectual disability (61.4% of the ODD cohort).

The propensity score-matched kidney transplant recipients cohort included 629 adults with IDD and 629 adults without IDD. Median age was 37 years and approximately 33% were male. Other/unspecified intellectual disability was the IDD diagnosis in approximately 45% of the cohort, and 22.7% had cerebral palsy.

In the matched ESKD cohort, 19.9% of adults with IDD (n=2125) were evaluated by a transplant surgeon, compared with 30.6% of adults without IDD (n=3271). Results of multivariable analysis demonstrated that the odds of being evaluated by a transplant surgeon were 54% lower for adults with IDD compared with those without IDD (odds ratio [OR], 0.46; 95% CI, 0.43-0.50).

In the matched cohort with ESKD, 5.9% of adults with IDD (n=633) received a kidney transplant, compared with 12.8% of adults without IDD (n=1367). In multivariable analysis, the odds of receiving a kidney transplant were 62% lower in adults with IDD compared with adults without IDD (OR, 0.38; 95% CI, 0.34-0.42). In addition, in a subset of patients who were evaluated by a transplant surgeon, 29.4% of adults with IDD (n=624) received a transplant compared with 41.2% of adults without IDD (n=1357) who received a transplant. In multivariable analysis, those with IDD had 51% lower odds (OR, 0.49; 95% CI, 0.43-0.55) of receiving a transplant compared with those without IDD.

In the propensity score-matched cohort of transplant recipients, 30.5% (n=383) experienced a perioperative complication, 40.0% (n=503) had a 90-day readmission, 7.7% (n=97) experienced a graft rejection within 1 year, and 1.8% (n=22) experienced a graft failure within 1 year. There was no statistical difference between the groups with and without IDD in the rates of postoperative adverse outcomes. Patients without IDD had similar rates of perioperative mortality (29.4% [n=185] vs 31.6% [n=199]), 90-day readmission (38.8% [n=244] vs 41.2% [n=259]), and graft failure within 1 year (numbers censored due to cell size restrictions). In multivariable analysis, IDD was not a risk factor for perioperative complications, 90-day readmission, or 1-year graft rejection.

The researchers cited some limitations to the study findings, including the possibility that some adults with IDD were excluded from the IDD cohort because they did not have an observed encounter during 2003 through 2020 with an IDD diagnosis, resulting in some adults with IDD incorrectly being included in the control cohort of adults without IDD. Other limitations were lack of data on whether the kidney donors were living or deceased, creating an inability to control for the difference in the analyses; the lack of psychosocial variables indicative of transplant appropriateness in the Medicare data; the inability to examine adequacy of postoperative care and treatment adherence; and the inability to assess the number of beneficiaries (with or without IDD) who chose not to move forward following the transplant evaluation process despite being offered the opportunity to do so.

In conclusion, the authors said. "There is growing national momentum to enact and enforce policies to improve equitable access to organ transplant for people with IDD and other disabilities. Like peers without IDD, some adults with IDD may not be strong candidates for transplant. However, adults with IDD deserve (and legally have the right to) equal access to evaluation and full holistic consideration as to whether they would be good transplant candidates. Our findings show that adults with IDD were significantly less likely to be evaluated for or receive kidney transplants than propensity score-matched peers without IDD. Using the largest US cohort of adult transplant recipients with IDD to date, we found that perioperative, 90-day, and 1-year kidney transplant outcomes were similar for adults with and without IDD and underscore the urgent need for antidiscrimination initiatives to promote the receipt of equitable care for this population." ■

TAKEAWAY POINTS

- Researchers reported results of a retrospective cohort study comparing rates of kidney transplant and transplant-specific outcomes between groups of adults with end-stage kidney disease with and without co-occurring intellectual and developmental disabilities (IDD).
- The rates of evaluation for kidney transplant by a transplant surgeon were lower in the cohort with IDD than in the cohort without IDD: 19.9% versus 30.6%, respectively. The odds of being evaluated by a transplant surgeon were 54% lower for adults with IDD.
- The rates of receipt of a kidney transplant were lower among adults with IDD than among adults without IDD (5.9% vs 12.8%, respectively). The odds of receiving a transplant were 62% lower among adults with IDD.

Kidney Transplant Outcomes in a Population of Undocumented Immigrants

In 2014, of the estimated 11 million undocumented immigrants living in the United States, 2.6 million lived in California. Of those 2.6 million, approximately 6500 had end-stage kidney disease (ESKD). The Emergency Medical Treatment and Active Labor Act provides treatment, including dialysis, in the event of an acute, life-threatening condition at Medicare-participating hospitals. However, in most states outpatient maintenance dialysis is not covered for undocumented immigrants. Further, despite both maintenance dialysis and kidney transplant being more cost-effective options and offering better outcomes than emergency-only dialysis, Medicare does not cover those costs for undocumented immigrants.

California is one of only a few states to use state funds to provide undocumented immigrants with access to maintenance dialysis and kidney transplant. There is a perception among health care workers that due to language barriers and lack of access to immunosuppressive medications and health care, undocumented immigrants have a higher risk of transplant failure compared with US residents. **Natsuki Eguchi, BS,** and colleagues at the University of California, Irvine, conducted a study to assess outcomes of kidney transplant among undocumented immigrants at the center. Results were reported online in *JAMA Network Open* [doi:10.1001/jamanetworkopen.2022.54660].

The single-center, retrospective cohort study was conducted between January 1, 2012, and September 1, 2019. Patients who received a kidney transplant at the University of California, Irvine, during the study period were included. Data analysis occurred from October 2020 to August 2021. The study exposure was citizenship status. Undocumented immigrants were defined as immigrants residing in the United States without permission or legal documentation.

The primary end point was all-cause graft loss, defined as the return to dialysis, need for second kidney transplant, or death. Secondary end points included all-cause mortality and acute kidney allograft rejection. Multiple Cox proportional hazard regression analysis was used to compare all-cause mortality between the two study groups (US residents and undocumented immigrants). Other outcomes, including all-cause graft loss and acute rejection, were assessed by competing risks regression with mortality and mortality plus graft loss serving as competing risks, respectively.

During the study period, 446 patients received a kidney transplant at the University of California. Mean age was 47 years, 59% (n=261) were male, and 26% (n=114) were undocumented immigrants. Compared with US residents, those in the undocumented immigrant group were younger and less likely to have pretransplant diabetes. Half of the US resident cohort was Hispanic while up to 95% of the undocumented immigrant cohort was Hispanic. The two groups were similar in dialysis modality; however, duration of dialysis in the undocumented immigrant group was significantly longer (mean, 6.00 in the US resident group vs 7.10 in the undocumented immigrant group; *P*=.04). Five percent of patients in the US resident group received a preemptive transplant, compared with no patients in the undocumented immigrant group.

Patients in the undocumented immigrant group were less likely to undergo living donor kidney transplant (30% in US residents vs 18% in undocumented immigrants; *P*=.02). Cold ischemic times were longer in the deceased donor kidneys in the undocumented immigrant group compared with US residents.

Median follow-up was 3.39 years. During follow-up, 48 US residents and six undocumented immigrants experienced all-cause graft loss. In the US resident group, 24 of the 48 graft losses were identified as dialysis after graft loss; four of the six losses in the undocumented immigrant group were dialysis after graft loss.

At 8 years posttransplant, graft survival was 86% in the US resident group and 95% in the undocumented immigrant group. During the 8-year period after transplantation, 26 in the US resident group and two in the undocumented immigrant group died, for an 8-year survival rate of 92% and 98%, respectively. Biopsy-proven rejection was seen in 36 patients in the US resident group and nine in the undocumented immigrant group.

In unadjusted analysis, US residents had a 192% increased risk for all-cause graft loss compared with undocumented immigrants (hazard ratio [HR], 2.92; 95% CI, 1.25-6.85; *P*=.01). When adjusted for recipient demographics, comorbidities, and/or transplant characteristics, the results were slightly attenuated but remained statistically significant. When stratified for deceased donor kidney transplant, a 184% increased risk for all-cause graft loss remained among US residents (HR, 2.84; 95% CI, 1.11-7.22; *P*=.02). Following adjustment for age, ethnicity, or delayed graft function, the increased risk became nonsignificant.

Although there was no difference between the two groups in dialysis after graft loss, the US resident group had a 343% increased risk for all-cause mortality (HR, 4.43; 95% CI, 1.05-18.69; *P*=04). Following stratification for deceased donor kidney transplant, the difference became nonsignificant.

There was no significant difference between the two groups in the incidence rate of kidney allograft rejection: US residents, 3.5 per 100 person-years versus undocumented immigrants, 2.4 per 100 person-years; rate ratio, 1.45 (95% CI, 0.90-5.05; *P*=.08).

The researchers cited some limitations to the study, including the single-center design, the small sample size, the possibility of several residual confounding factors, and the inability to account for genetic factors.

In summary, the authors said, "No significant difference in mortality, dialysis after graft loss, and rejection were evident among the US resident and undocumented immigrant groups. However, the undocumented immigrant group did exhibit an insignificant reduced risk for all-cause mortality, which was likely due to their younger age. In conclusion, the kidney transplant outcomes of the undocumented immigrants are not inferior to those of the US residents; however, the undocumented immigrants have long been a minority in kidney transplant in the United States. Extending kidney transplant to undocumented immigrants may be a reasonable option to offer better ESKD outcomes to this undeserved population." ■

TAKEAWAY POINTS

- Researchers reported results of a study to compare outcomes of kidney transplant in a population of undocumented immigrants with those in a population of US residents at an academic medical center in California.
- The primary end point of interest was all-cause graft loss. Secondary end points were all-cause mortality and rejection.
- There were no significant differences between the two groups in mortality, dialysis after graft loss, and rejection. The undocumented immigrant group did exhibit an insignificant reduced risk for all-cause mortality.

NKF Names Jamie Herrera Beutler to Board of Directors

In a recent press release, the National Kidney Foundation (NKF) announced the appointment of **Jaime Herrera Beutler** to the NKF National Board of Directors. Ms. Herrera Beutler is a former member of the US Congress and of the Washington state legislature.

Jaime Herrera Beutler

Tracy McKibben, NKF board chair, said, "We are very excited that Jamie has joined the NKF Board of Directors and brings over 15 years of knowledge and expertise in building and leading bipartisan coalitions that delivered key legislative victories for maternal health care, environmental protection, energy, timber, and medical care for children. Jamie brings experience in bridging the gaps between policies and laws around health care and the families they impact. She also has a very inspiring connection to kidney disease. We look forward to working with her as we build greater awareness of kidney disease and ways to achieve optimal kidney health."

Ms. Herrera Beutler said, "As the mother of a child who received a kidney transplant before she was three years old, I feel blessed that my husband was able to provide our first-born daughter with the gift of life. I'm honored to join NKF's Board of Directors and share my story and expertise with the largest kidney organization in the country because far too many people knowingly and unknowingly struggle with kidney disease."

Treating Patients With ESRD and Atrial Fibrillation

In honor of National Kidney Month, Cadrenal Therapeutics, Inc. issued a press release highlighting the company's goal to advance tecarfarin, a novel therapy for the prevention of systemic thromboembolism of cardiac origin in patients with end-stage renal disease (ESRD) and atrial fibrillation (AF). Tecarfarin has been granted orphan drug and fast track designations from the US Food and Drug Administration (FDA) for use in that patient population. Tecarfarin is a vitamin K antagonist oral anticoagulant specifically designed to leverage the advantages of warfarin while avoiding its pitfalls, according to the press release.

In patients with ESRD, the presence of AF nearly doubles the risk of mortality and increases the risk of stroke by approximately five-fold. Studies have suggested that AF is an independent risk factor for developing ESRD in patients with chronic kidney disease. Both diseases share common risk factors, including hypertension, diabetes, vascular disease, and advancing age.

Quang Pham, founder and CEO of Cadrenal Therapeutics, said, "The presence of either chronic kidney disease or AF increases the risk of serious thromboembolic adverse clinical outcomes, such as stroke and death. Antithrombotic therapy is typically recommended to decrease this risk in AF patients, but unfortunately, there are no approved therapies for patients who have ESRD with AF. Cadrenal hopes tecarfarin can be the answer for this group of patients who carry high morbidity rates and exorbitant costs to the American health care system due to lack of effective treatment.

"We are currently planning a phase 3 clinical trial for tecarfarin based on feedback received by the FDA. We look forward to working closely with the FDA to evaluate this therapy as a potential new treatment option for this severely underserved patient population."

Monogram Health Names COO

In a recent press release, Monogram Health announced the appointment of **Casey McKeon** as chief operating officer (COO). Monogram Health is a specialty provider of in-home, evidence-based care and benefit management services for people living with chronic kidney disease and related metabolic disorders. Prior to joining Monogram, Mr. McKeon served as general manager of strategy and operations for Cigna's government business segment.

Casey McKeon

Mike Uchrin, Monogram Health CEO, said, "Casey is a demonstrated leader with notable experience driving systemic growth and operational efficiency. His extensive background managing complex health plan programs for patients with complex conditions—combined with his focus on delivering results that improve quality and affordability for patients and providers alike—deeply aligns with our own mission and vision of transforming kidney and polychronic care delivery across America."

"I have been impressed with Monogram's rapid growth and noble mission since my first exposure to the company," Mr. McKeon said. "Their innovative model is truly transforming care delivery and improving quality of life for tens of thousands of Americans navigating multiple chronic diseases. I am proud to become part of the team and look forward to contributing to the company's continued success."

Topline Results of Phase 3 NeflgArd Trial

In a recent press release, Calliditas Therapeutics announced topline data from the phase 3 NeflgArd trial evaluating Nefecon (marketed as TARPEYO® [budesonide] delayed-release capsules in the United States) for patients with IgA nephropathy. The trial met its primary end point, demonstrating a statistically significant benefit over placebo ($P<.0001$) in estimated glomerular filtration rate (eGFR) over the 2-year study period of 9 months of treatment with budesonide or placebo and 15 months of follow-up off drug. Supportive 2-year total slope analyses were statistically significant and clinically meaningful, reflecting a sustained treatment benefit.

Jonathan Barratt, PhD, FRCP, Mayer Professor of Medicine (Nephrology) at Leicester University, Leicester, England, said, "These data show the kidney function protection delivered by Nefecon and demonstrate that the approach offers patients a truly disease modifying treatment with sustained reductions in proteinuria over 2 years and continued eGFR benefit. Importantly, Nefecon was well tolerated, and together with the proteinuria and eGFR data, mean that Nefecon has cemented its place as a key treatment option for patients with IgA nephropathy at risk for progression kidney function loss."

Richard Philipson, MD, chief medical officer at Calliditas, said, "I am delighted with the positive outcome of the NeflgArd trial. This important milestone is the culmination of many years of hard work and dedication from so many people involved in the study. I would like to extend my thanks in particular to the investigators and site staff involved in the study, as well as of course the participating patients."

Calliditas plans to file for full approval from the US Food and Drug Administration, and support filing for full approval with the European Commission and the United Kingdom Medicines and Healthcare products Regulatory Agency during 2023 for patients with primary IgA nephropathy based on the phase 3 study population.

Get Uncomfortable Campaign Aims to Protect Kidneys

Aurinia Pharmaceuticals has launched the Get Uncomfortable campaign to educate and motivate people living with lupus nephritis to protect their kidneys by visiting their physician and undergoing routine testing to help prevent irreversible kidney damage. **Toni Braxton,** the seven-time Grammy Award-winning singer, songwriter, actress, producer, and entrepreneur, will share her story of life

with lupus and managing her kidney health to prevent life-threatening complications.

In a press release from Aurinia, Ms. Braxton said, "Getting routine urine tests and seeing a doctor regularly is so important because up to 30% of people with lupus who have kidney involvement will experience kidney failure...During the past 15 years, I've learned to prioritize my kidney care and to be a strong advocate for my health, and I'm speaking our now to encourage other women to do the same."

Peter Greenleaf, Aurinia president and CEO, said, "As part of our ongoing commitment to raising awareness for lupus nephritis, we are thrilled to partner with Toni Braxton on the Get Uncomfortable campaign. Since launching in October 2022, the Get Uncomfortable campaign has reached thousands of patients with important information about routine urine testing and treatment options to support informed discussions with their health care team. Toni's relatable and authentic story about living with lupus will further inspire people living with lupus nephritis to better understand their health risks and take action to protect their kidneys before it's too late."

AKF Supports Living Donor Protection Act of 2023

In late spring, the American Kidney Fund (AKF) announced support for the introduction of the federal Living Donor Protection Act of 2023 (HR 2923). The bill aims to support job protections for living organ donors and to certify that insurance companies cannot decline or limit specific insurance coverage due to an individual's status as a living organ donor.

The bipartisan legislation was previously introduced in 2021, 2019, 2017, 2016, and 2014. It prohibits insurers from denying or canceling coverage, refusing to issue coverage, changing the price of coverage, or otherwise altering any condition of life insurance, disability, or long-term care insurance policy issued for an individual based on living donor status.

LaVarne A. Burton, president and CEO of AKF, said, "By passing the Living Donor Protection Act of 2023, Congress would reduce the barriers people face in becoming living donors and giving an organ to someone in need. This legislation would save lives. I want to thank out champions in Congress for introducing this important bill on behalf of the hundreds of thousands of people living with kidney failure in the United States and their loved ones."

The 2023 act was introduced by Rep Jerrold Nadler (D-NY), Rep Troy Balderson (R-OH), Rep Lisa Blunt Rochester (D-DE), Rep Jim Costa (D-CA), Rep John Curtis (R-UT), Rep Diana DeGette (D-CO), Rep Mariannette Miller-Meeks (R-IA), and Rep Gregory F. Murphy (R-NC), joined by Sen Kirsten Gillibrand (D-NY) and Sen Tom Cotton (R-AR).

Diality Names Robert Funari to Board

Diality, Inc. has named **Robert Funari** to its Board of Directors. Diality is a medical technology company working to develop a smart, flexible hemodialysis platform.

According to a press release, Mr. Funari has nearly 50 years' experience in the health care industry, working in the fields of services and medical devices. **Osman Khawar, MD,** Diality CEO, said, "Robert has an outstanding half-century record of brining his knowledge and strategic thinking to bear on the constantly evolving health care market. His insights will be invaluable as we prepare to bring our new hemodialysis system to market to empower kidney care providers while prioritizing patient care and quality of life."

Diality's system is designed to be versatile for any care setting. The compact footprint and an intuitive user interface are designed to enable the system to be ceasily integrated with and transported within any dialysis setting, including acute-care hospitals, dialysis clinics, transitional care units, traditional home environments, or skilled nursing facilities.

Mr. Funari said, "Diality's novel approach to developing an extremely flexible hemodialysis system interested me from the start. I look forward to working with the strong leadership team [Dr.] Osman has assembled to help bring its mission of improving lives impacted by kidney disease to fruition."

Waldon Biosciences Doses First Subject in Phase 1 Trial

Walden Biosciences, Inc. has announced that the first subject was dosed in the company's phase 1 clinical trial of WAL0921 in healthy subjects. WAL0921 is a first-in-class, proprietary, humanized monoclonal antibody that binds soluble urokinase plasminogen activator receptor (suPAR), inhibiting the proinflammatory action that causes podocyte dysfunction and renal disease.

In a press release from Walden Biosciences, **Blaine H. McKee, PhD,** CEO, said, "Dosing the first subject in this first human study with WAL0921 is a meaningful milestone for Walden Biosciences that marks our transition to a clinical development company and brings us one step closer to our goal to transform the treatment of kidney disease. Elevated levels of suPAR inflame kidney tissues leading to chronic injury, loss of podocytes, proteinuria, and compromise the whole kidney structure and function, leading ultimately to end-stage renal disease in these patients. WAL0921 is designed to directly target this causal agent driving renal disease to provide a truly novel and disease-modifying approach for many chronic kidney diseases."

The phase 1 clinical trial is a single-center, placebo-controlled, single ascending dose escalation study in five cohorts evaluating the safety, pharmacokinetics, and pharmacodynamics of WAL0921 in up to 40 healthy volunteers. ■

CONFERENCE COVERAGE KIDNEY WEEK 2022

Daprodustat Versus Epoetin Alfa for Anemia in Hemodialysis Patients

Among patients treated with anemia of chronic kidney disease (CKD) there are correlations between higher doses of erythropoiesis-stimulating agents (ESAs) and morbidity. Daprodustat is a hypoxia-inducible factor prolyl hydroxylase inhibitor that corrects anemia via introduction of endogenous erythropoietin (EPO). **Daniel W. Coyne, MD,** and colleagues conducted a study comparing daprodustat with epoetin alfa to treat anemia in patients on maintenance hemodialysis. The outcomes of interest were changes in EPO and vascular endothelial growth factor (VEGF).

Results of the double-blind trial were reported during poster session at the ASN Kidney Week 2022. The poster was titled *Maximal Change in Erythropoietin in Hemodialysis Patients Receiving Daprodustat of Epoetin Alfa in the ASCEND-TD Trial.*

The study cohort included 407 patients on ESA with baseline hemoglobin 8-11.5 g/dL. Participants were randomized 2:1 to daprodustat three times a week or epoetin once a week or three times weekly for 52 weeks (ASCEND-TD NCT03400033). The primary end point (change in hemoglobin) was met and safety profiles were similar. Predose plasma EPO and VEGF were measured on day 1 and once during weeks 28 to 52, predose and 2, 4, 6, or 8 hours postdose. Major adverse cardiovascular events (MACE) were adjudicated.

Mean baseline EPO levels were low (22 IU/L in the daprodustat arm vs 18 IU/L in the epoetin arm). Across all doses, maximal mean EPO increases were lower with daprodustat (161) versus epoetin (12313). Higher daprodustat and epoetin doses correlated with maximal EPO; maximal postbaseline and change from baseline EPO with higher daprodustat doses (20-48 mg) were similar to or lower than for the lowest epoetin dose (1500 U).

VEGF levels declined from baseline for both daprodustat and epoetin, unrelated to dose. Daprodustat was not correlated to occurrence of the first MACE; mean dose at first MACE was similar to final dose without MACE.

"Daprodustat-induced changes in EPO were dose-dependent. Despite high daprodustat doses, the EPO levels produced were similar to levels seen at the lowest epoetin doses," the authors said.

Source: Coyne DW, Wanner C, Lopes RD, et al. Maximal change in erythropoietin in hemodialysis patients receiving daprodustat or epoetin alfa in the ASCEND-TD trial. TH-P0690. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2022; November 3, 2022; Orlando, Florida. Funding was provided by GSK.

Abstract Roundup

COVID-19

Glomerular Diseases Associated With COVID-19

Kidney International Reports. doi.org.1016/j.ekir.2023.03.016

COVID-19 is a systemic disease that targets multiple organs; the kidney is one of the target organs of infection related to COVID-19. Kidney injury has been reported in up to 40% of patients with COVID-19, and several glomerular diseases have been reported in association with COVID.

Nattawat Klomijit, MD, and colleagues provided an overview of glomerular diseases that have been reported frequently among patients with COVID-19 that have a mechanistic explanation that indicates the likelihood of being related to the virus. Collapsing glomerulopathy (CG) is the most prevalent glomerular disease related to COVID-19. The association between CG and COVID-19 has led to coining of a proposed term, COVID-19 associated nephropathy (COVAN).

High-risk APOL1 genotypes are the primary risk factor for COVAN patients. Other complications include podocytopathy, membranous nephropathy, pauci-immune crescentic glomerulonephritis, and thrombotic microangiopathy.

CG is the most common glomerular pathology in kidney allografts. Patients generally present with acute kidney injury or abnormal urinary findings at the time of or shortly after a diagnosis of COVID-19. Management of glomerular disease in transplant recipients with COVID-19 is challenging. Providers should balance the risk and benefits of immunosuppression, particularly in patients with active diseases. Short-term outcomes vary but are generally poor with high morbidity and mortality.

In summary, the researchers said, "Future study of long-term outcomes is needed to improve our understanding of glomerular disease associated with COVID-19."

Plasma Biomarkers as Predictors of MAKE in Patients With COVID-19

American Journal of Kidney Diseases. doi.org/10.1053/j.ajkd.2023.03.010

The risk for major adverse kidney events (MAKE) is increased among patients hospitalized with COVID-19. **Steven Menez, MD, MHS,** and colleagues conducted a prospective cohort study to identify plasma biomarkers predictive of MAKE in that patient population. The cohort included 576 patients hospitalized with COVID-19 between March 2020 and January 2021 across three academic medical centers.

Outcomes of interest were major adverse kidney events, defined as kidney Disease: Improving Global Outcomes stage 3 acute kidney injury (AKI), AKI requiring dialysis, or mortality up to 60 days. The study exposures were 26 plasma biomarkers in injury, inflammation, and repair from first available blood samples collected during hospitalization.

Median length of stay for COVID-19 hospitalization was 9 days. Of the total cohort, 16% (n=95) experienced MAKE. There was a significant association between each 1-standard deviation increase in soluble tumor necrosis factor receptor 1 (sTNFR1) and sTNFR2 and an increased risk of MAKE (adjusted hazard ratios, 2.30; 95% CI, 1.86-2.85 and 2.26; 95% CI, 1.87-2.95, respectively). The C-index of sTNFRI1 alone was 0.80 (95% CI, 0.78-0.84), while the C-index of sTNFR2 was 0.81 (95% CI, 0.77-0.84). Least absolute shrinkage and selection operator and random forest regression modeling using all biomarkers yielded C-indices of 0.86 (95% CI, 0.83-0.89) and 0.84 (95% CI, 0.78-0.91), respectively.

In summary, the authors said, "TNFR1 and sTNFR2 are independently associated with MAKE in patients hospitalized with COVID-19, and can both also serve as predictors for adverse kidney outcomes."

ADPKD

Tolvaptan To Treat Patients With Rapidly Progressing ADPKD

Korean Journal of Internal Medicine. doi:10,3904/kjm.2022.376

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disease with few therapeutic options. Tolvaptan, a vasopressin 2 receptor antagonist, has emerged as a treatment strategy and disease-targeted approach for patients with rapid progression of ADPKD.

Results of recent trials of tolvaptan have demonstrated significant efficacy in preserving kidney function and reduction of the growth rate of total kidney volume (TKV). In patients with more severe clinical phenotypes such as higher TKV and rapid decline in kidney function, the results were more pronounced. Side effects include aquaretic symptoms related to the mechanism of the drug and directly related to patient quality of life have been shown.

According to **Yaerim Kim, MD,** and **Seungyeup Ham, MD, PhD,** the development of a shared decision-making process aimed at reducing the incidence of side effects and improving medication adherence could be a valuable tool in treating patients with rapidly progression ADPKD. The researchers provided a review of overall clinical trials for the use of tolvaptan in the patient population and suggested factors to consider during the shared decision-making process regarding treatment strategy.

DIABETES

Mechanisms of Renoprotective Effects of SGLT2 Inhibitors

Frontiers in Medicine. doi.org/10.3389/fmed.2023.1115413

Patients with chronic kidney disease (CKD) treated with a sodium glucose cotransporter 2 (SGLT2) inhibitor have reduced risk of adverse renal outcomes independent of changes in blood glucose concentrations and blood pressure. However, according to **Akira Nishiyama, MD, PhD,** and **Kento Kitada, PhD,** of the Department of Pharmacology, Faculty of Medicine, at Kagawa University, Takamatsu, Japan, the precise mechanism responsible for the SGLT2 inhibitor-induced renoprotective effect is unclear.

It has been shown that SGLT2 inhibitors induce antihypertensive effects with decreased sympathetic nerve activity associated with transient natriuresis. In addition, SGLT2 inhibitor treatment produces vascular endothelial growth factor-a in the renal tubules, improving renal ischemia. Results of other studies have suggested there may be an association between ketone body production, changes in glomerular hemodynamics, and intrarenal metabolic changes and a reduction in oxidative stress due to decreased tubulointerstitial glucose levels and the renoprotective effects of SGLT2 inhibitors.

In a recent review, the researchers summarized the mechanism responsible for the renoprotective effects of treatment with SGLT2 inhibitors and tested a hypothesis regarding an "aestivation-like response," which is a biological defense response to starvation.

DIALYSIS

Serum Phosphate Levels and Morality Risk

Kidney 360. 2023;4(3):374–380

Results of previous studies have shown that serum phosphate levels have a bidirectional relation to outcome among patients receiving maintenance dialysis. According to **Karlien J. ter Meulen, MD,** and colleagues at Maastricht University Medical Center, The Netherlands, there are few data available on the relation between temporal dynamics of serum phosphate in relation to outcome. The researchers reported results of a study designed to examine the relation between variability of serum phosphate and all-cause mortality.

The study included all adult incident hemodialysis patients treated in Fresenius Kidney Care clinics in the United States between January 2010 and October 2018. Baseline was defined as 6 months following hemodialysis initiation and months 7 to 18 were defined at the follow-up period. All-cause mortality was recorded during follow-up. The association between phosphate, directional range (DR), and all-cause mortality was examined using Cox proportional models with spline terms. The interactions of phosphate, DR, and

all-cause mortality were further delineated using tensor product smoothing splines.

The analysis included 302,613 patients. At baseline, phosphate was 5.1 mg/dL, and mean DR was +0.6 mg/dL. Across varying levels of phosphate, there was an association between higher levels of DR of phosphate and a higher risk of all-cause mortality. The negative DR effect was most pronounced in patients with lower levels of phosphate and serum albumin. A positive DR was associated with increased mortality in patients with higher phosphate levels.

In conclusion, the authors said, "Higher variability of serum phosphate is related to mortality at all levels of phosphate, especially in lower levels with a negative DR and in low serum albumin levels. This could possibly reflect dietary intake in patients who are already inflamed or malnourished, where a further reduction in serum phosphate should prompt for nutritional evaluation."

Detecting Needle Dislodgments During Hemodialysis

Kidney 360. 2023;4(4):e476-e485

Hemodialysis venous needles may become dislodged in some rare instances, and, when left undetected, can lead to injury or death. Dialysis machines have alarms to detect various needle dislodgement (VND). However, according to **Stanley Frinak, MD,** and colleagues, the range of detection is limited. Understanding clinical conditions that may lead to missed needle dislodgements will aid in development of more robust detection systems.

The researchers created a sham dialysis circuit with a Fresenius 2008K dialysis machine for in vitro simulation testing of machine alarm behavior under various conditions. The circuit used a blood substitute and mimicked a patient's venous access site. The rate of blood flow, venous pressure (VP), and upward drift in VP were varied, and the time to alarm for the machine was analyzed, leading to an improved algorithm. They also conducted a cross-sectional retrospective study to identify the clinical occurrence of VP upward drift between September 1, 2016, and November 1, 2016, in a cohort of patients receiving hemodialysis with an arteriovenous fistula.

The analysis included 43,390 VP readings for 147 patients receiving hemodialysis. Of those, 38% (n=16,594) showed an upward drift in VP, with a mean increase of 11 mm Hg within 20 minutes. Nineteen VND simulations under different VP and blood flow parameters resulted in 19 algorithm alarm activations. Only eight simulations activated a machine alarm. Machine alarm activation time was longer than the algorithm time for all eight machine alarms.

"Patients can experience changes in VP during hemodialysis which may not trigger a machine alarm in the case of a VND. Our simulations showed that current dialysis machine alarm systems may not compensate for upward drift in

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Print-only Content

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VP, and improved algorithms for detecting needle dislodgment during hemodialysis are needed," the researchers said.

HYPERKALEMIA

Social Determinants of Health and Adherence to Patiromer

PLOS One. doi.org/10.1371/journal.pone.0281775

Patients with chronic kidney disease commonly develop hyperkalemia, a serious and frequent complication that can negatively affect continuation of beneficial evidence-based therapies. Recent developments in the treatment of chronic hyperkalemia in patients with CKD include patiromer. According to **Nathan Kleinman, PhD,** and colleagues, the optimal use of therapies such as patiromer depends on patient adherence.

Social determinants of health (SDOH) are key and may have an impact on medical conditions as well as adherence to prescription medications. Dr. Kleinman et al conduced an analysis to examine the association between SDOH and adherence to or nonuse of patiromer for the treatment of hyperkalemia.

The observational, retrospective, real-world claims analysis included adults with prescriptions for patiromer and available prescription data for 6 and 12 months pre- and postindex prescription data. Prescription data were obtained from Symphony Health's Dataverse during 2015 to 2020. Information on SDOH was gathered from census data. Subgroups included patients with heart failure, hyperkalemia-confounding prescriptions, and any CKD stages.

Adherence was defined as >80% of proportion of days covered (PDC) for ≥60 days and ≥6 months. Abandonment of patiromer was defined as a portion of reversed claims. Logistic regression controlling for similar factors and initial days' supply were used to define abandonment models.

At 60 days, 48% of patients had a patiromer PDC >80%. At 6 months, 25% met that definition. There were associations between higher PDC and older age, male sex, Medicare/Medicaid coverage, prescription from a nephrologist, and receiving renin-angiotensin-aldosterone system inhibitors. There were correlations between lower PDC and higher out-of-pocket costs, unemployment, poverty, disability, and any CKD stage with comorbid heart failure. Regions with higher education and income levels had better PDC.

In summary, the authors said, "SDOH (unemployment, poverty, education, income) and health indicators (disability, comorbid CKD, heart failure) were associated with low PDC. Prescription abandonment was higher in patients with prescribed higher dose, higher out-of-pocket costs, those with disability, or designated White. Key demographic, social, and other factors play a role in drug adherence when treating life-threatening abnormalities such as hyperkalemia and may influence patient outcomes." ■

Sarah Tolson

The Digital Revolution in Nephrology: Shaping the Future of Renal Care

In recent years, technological advances have started to reshape the nephrology landscape, propelling both health care providers and administrative professionals into a new era of patient care. As adoption of digital health accelerates, driven by the pandemic and the burgeoning demand for remote health care, understanding its influence and implications is pivotal for renal care practitioners and administrative teams alike.

First, telemedicine has emerged as a game-changer in nephrology. Notably, in the management of chronic kidney disease (CKD) that demands frequent patient-doctor interaction, the convenience of virtual consultations cannot be overstated. Telemedicine eliminates geographical barriers, reducing travel times and associated stress for patients. It also extends the reach of nephrologists to rural areas, ensuring patients in remote locations receive much needed care. However, challenges persist. Technological literacy, both among providers and patients, can present a barrier, and the creation of a robust, patient-centric virtual care model remains a work in progress. During the height of the pandemic, many of the providers I know utilized telemedicine in some form. While technological literacy was a barrier for audiovisual calls, so was access to the internet or equipment capable of audiovisual encounters.

Simultaneously, the introduction of artificial intelligence (AI) and machine learning (ML) into renal care has transformative potential. These technologies are making strides in early detection and prognosis of renal diseases, offering predictive insights that were previously unattainable. The use of AI and ML in individualized treatment planning can lead to improved patient outcomes and efficiency in care delivery. As this field matures, the need for nephrologists to acquire an understanding of AI and ML, their possibilities, and ethical considerations grows significantly.

Moving to administrative aspects, electronic health records (EHRs) have become an essential tool in nephrology practice management. Some of these systems have the potential to offer real-time, patient-centered records accessible to authorized users across the care continuum, aiding in coordinated and efficient care. Furthermore, advanced EHR systems can provide decision-making support based on analytics and best practice guidance, thereby enhancing the quality of care. However, successful EHR integration demands careful consideration of aspects such as data security, interoperability, and user training. Interoperability is a particular concern in nephrology practices as providers regularly see patients in the clinic, at the dialysis facility, and at the hospital. Because dialysis facilities and hospitals have their own EHRs, the health information for a CKD patient is often spread through at least two or three EHRs, making it significantly more challenging to fully optimize an EHR.

As renal care becomes increasingly digitized, data security and patient privacy are thrust into the spotlight. The shift toward digital health has given rise to new regulations aimed at protecting patient data and ensuring ethical technology use. Thus, health care providers and administrative professionals must remain vigilant and informed about the evolving legal landscape. Compliance with regulations such as HIPAA in the United States is non-negotiable and is as critical as adopting the technologies themselves.

Lastly, the cost-effectiveness of digital health in nephrology is an area of growing interest. While the initial investment in digital health technology may be substantial, the potential for cost savings in the long term is significant. By enabling remote patient monitoring and reducing hospital readmissions, digital health can lead to substantial cost savings for the health care system as a whole. However, a comprehensive understanding of the implications, both from a time investment and financial perspective, is crucial to making informed decisions about digital health investment.

In conclusion, the digital revolution in nephrology presents many opportunities and challenges for health care professionals. Telemedicine, AI, ML, EHRs, and digital health regulations are not merely buzzwords but are shaping the future of renal care. It is a journey of constant learning and adaptation, and the ultimate beneficiary is the patient, who stands to receive more accessible, efficient, and personalized care. ■

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 interventional nephrology. 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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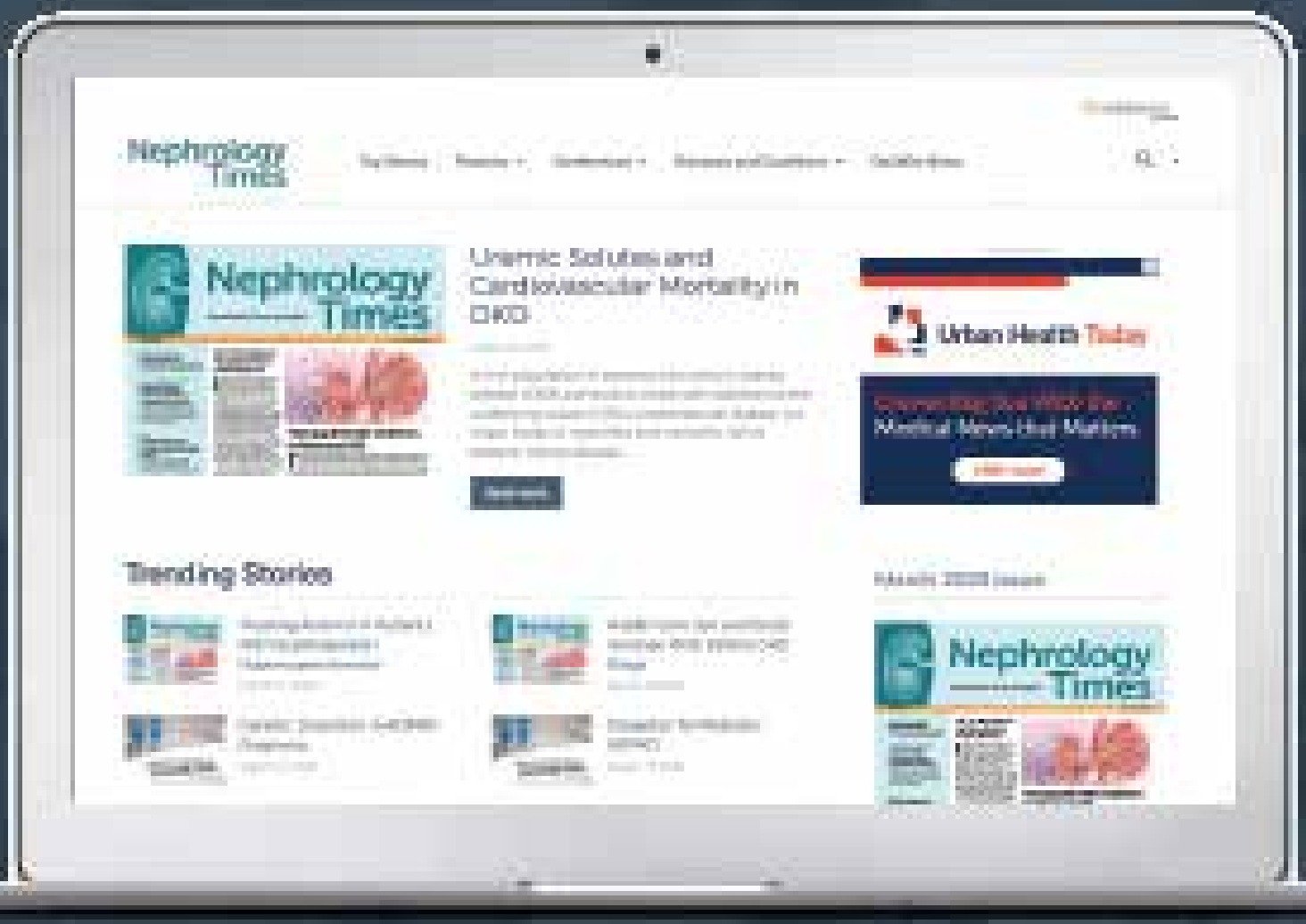

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