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Kidney News

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Focus on Community-Driven Prevention Helps Reduce ESKD in American Indian and Alaska Native Communities

By Bridget M. Kuehn

As a family physician and diabetes team lead in Juneau working for the Southeast Alaska Regional Health Consortium, Mary Owen, MD, could audit the care received by all of the diabetes patients served by her tribal clinic. The Special Diabetes Program for Indians (SDPI) funded this population-based approach through the Indian Health Service (IHS), which contracted with the clinic.

The audits allowed Owen, now director of the Center of American Indian and Minority Health at the University of Minnesota Medical School, to assess blood pressure and blood sugar control among patients and to gauge how many patients were receiving guideline-directed care. She could also compare her tribal clinic's results with other clinics in Alaska. If she saw that another community had better results, she could reach out and talk to them about what was working for them. "That has given us power," said Owen, who is also president of the Association of American Indian Physicians. "The other piece of SDPI that's phenomenal is that we are able to run these systems ourselves."

The community-driven focus of the SDPI has contributed to its lasting health benefits for Native American communities. Amid rising rates of end stage kidney disease (ESKD) nationally, American Indian and Alaska Native people experienced the lowest increases in the incidence of any racial or ethnic groups between 2000 and 2019, according to the US Centers for Disease Control and Prevention (CDC)'s *Morbidity and Mortality Weekly Report* (1). Cases of ESKD among American Indian and Alaska Native people increased about 25% during this period compared with a 42% increase in cases in the US overall. Other high-risk groups experienced dramatic escalations in incidence, including Asian (~150% increase), Native Hawaiian and other Pacific Islander (~97% increase), and Hispanic (84% increase) individuals. People of Black race experienced a 30% increase, and those of White race had a 33% increase.

The lead author of the CDC report (1), Nilka Ríos Burrows, MPH, an epidemiologist, recently with the Division of Diabetes Translation and head of the Chronic Kidney Disease (CKD) Initiative at the CDC, noted in an email interview that a variety of factors are contributing to rising rates of ESKD. These include a growing and aging US population; a high prevalence of risk factors, such as diabetes and hypertension; and better ESKD patient survival. However,

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Donor DNA Monitoring Can Detect Early Graft Injury

Recent research suggests a potential expanded role for monitoring of donor-derived cell-free DNA (dd-cfDNA) in the early identification of graft injury after kidney transplantation.

In the Assessing Donor-Derived Cell-Free DNA Monitoring Insights of Kidney Allografts with Longitudinal Surveillance (ADMIRAL) study, published in *Kidney International,* 1092 kidney transplant recipients were monitored for dd-cfDNA for 3 years after transplantation. The researchers used a targeted sequencing assay that quantified dd-cfDNA using highly polymorphic single nucleotide polymorphisms without the need for separate donor or recipient genotyping. The findings of 5873 dd-cfDNA measurements were analyzed for association with histologic evidence of allograft rejection. The analysis included 219 biopsy-paired dd-cfDNA results from 203 patients; 110 biopsies were performed for cause and 109 for surveillance.

Elevated dd-cfDNA of 0.5% or greater was correlated with clinical and subclinical allograft rejection. At this threshold, dd-cfDNA was associated with an increased risk of de novo donor-specific antibodies with a hazard ratio (HR) of 2.71. The elevated dd-cfDNA values occurred a median of 91 days before donor-specific antibodies were identified. Patients with two or more dd-cfDNA results over the 0.5% threshold were more likely to have a 25% decline in estimated glomerular filtration rate over 3 years with a hazard ratio of 1.97. An elevated dd-cfDNA result had a positive predic-

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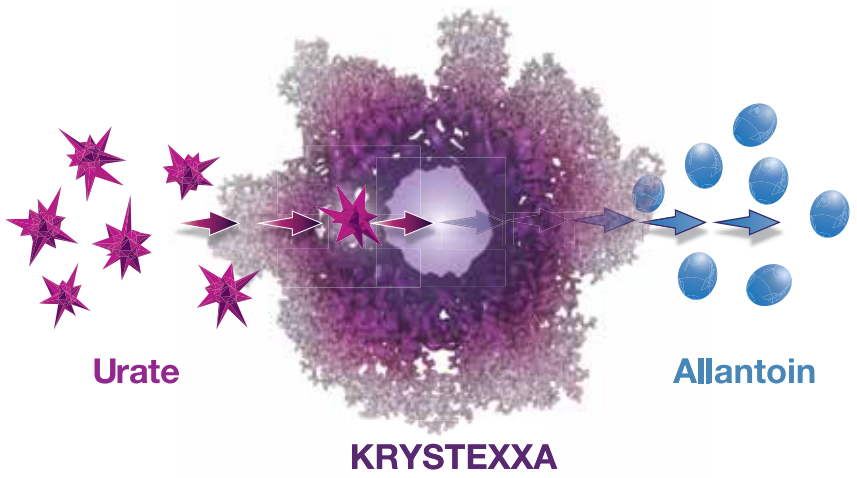
Inside

KRYSTEXXA (PEGLOTICASE) IS A RECOMBINANT INTO ALLANTOIN[1]



Artist's renditions.

RENAL EXCRETION OF ALLANTOIN IS UP TO 10 TIMES MORE EFFICIENT THAN EXCRETION OF URIC ACID[2]

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATIONS AND USAGE

KRYSTEXXA® (pegloticase) is indicated for the treatment of chronic gout in adult patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

Important Limitations of Use: KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

IMPORTANT SAFETY INFORMATION

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS

Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA. Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported. KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions. Patients should be premedicated with antihistamines and corticosteroids. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA. Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.

The risk of anaphylaxis and infusion reactions is higher in patients who have lost therapeutic response.

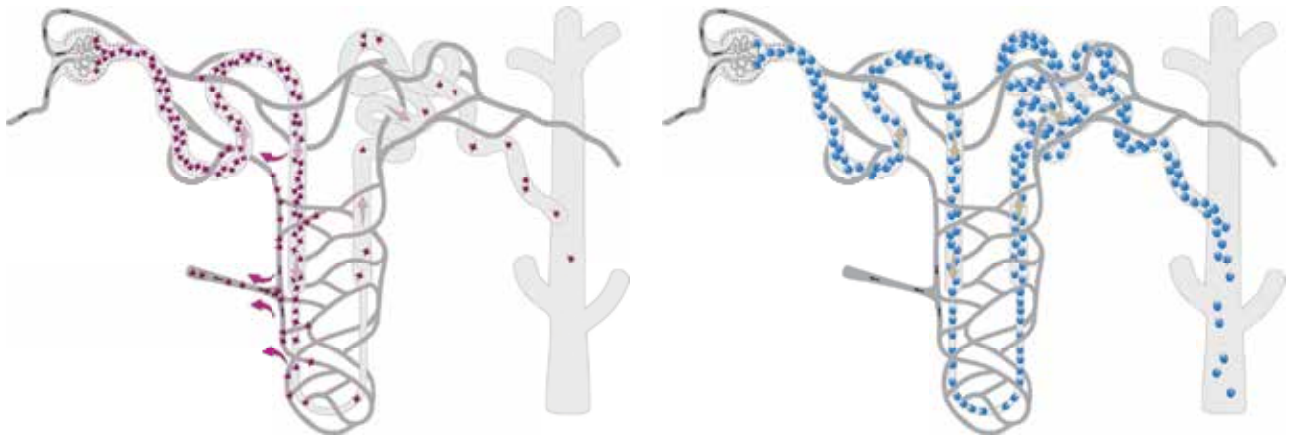
Concomitant use of KRYSTEXXA and oral urate-lowering agents may blunt the rise of sUA levels. Patients should discontinue oral urate-lowering agents and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

In the event of anaphylaxis or infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate.

References: 1. KRYSTEXXA (pegloticase) [prescribing information] Horizon. **2.** McDonagh EM, et al. *Pharmacogenet Genomics*. 2014;24:464-476. **3.** Terkeltaub R, et al. *Arthritis Res Ther*. 2006;8(suppl 1):S4.

HORIZON

URICASE ENZYME THAT CONVERTS URATE



Only 10% of uric acid filtered through the kidney is excreted[3]

vs

Nearly all of allantoin filtered through the kidney is excreted[2,3]

TO LEARN MORE, VISIT KRYSTEXXAHCP.COM

Inform patients of the symptoms and signs of anaphylaxis, and instruct them to seek immediate medical care should anaphylaxis occur after discharge from the healthcare setting.

CONTRAINDICATIONS: G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA

Screen patients for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. Do not administer KRYSTEXXA to these patients.

GOUT FLARES

An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including treatment with KRYSTEXXA. If a gout flare occurs during treatment, KRYSTEXXA need not be discontinued. Gout flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended starting at least 1 week before initiation of KRYSTEXXA therapy and lasting at least 6 months, unless medically contraindicated or not tolerated.

CONGESTIVE HEART FAILURE

KRYSTEXXA has not been studied in patients with congestive heart failure, but some patients in the clinical trials experienced exacerbation. Exercise caution when using KRYSTEXXA in patients who have congestive heart failure and monitor patients closely following infusion.

ADVERSE REACTIONS

The most commonly reported adverse reactions in clinical trials with KRYSTEXXA are gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis and vomiting.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for KRYSTEXXA on the following page.

KRYSTEXXA®
pegloticase

KRYSTEXXA® pegloticase

(pegloticase injection), for intravenous infusion

Brief Summary - Please see the KRYSTEXXA package insert for Full Prescribing Information.

WARNING: ANAPHYLAXIS and INFUSION REACTIONS; G6PD DEFICIENCY ASSOCIATED HEMOLYSIS and METHEMOGLOBINEMIA

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA.**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Patients should be pre-medicated with antihistamines and corticosteroids.**
- **Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**
- **Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. Do not administer KRYSTEXXA to patients with G6PD deficiency.**

INDICATIONS AND USAGE

KRYSTEXXA® (pegloticase) is a PEGylated uric acid specific enzyme indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.

Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

Important Limitations of Use:
KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

CONTRAINDICATIONS

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

WARNINGS AND PRECAUTIONS

Anaphylaxis

During pre-marketing clinical trials, anaphylaxis was reported with a frequency of 6.5% (8/123) of patients treated with KRYSTEXXA every 2 weeks and 4.8% (6/126) for the every 4-week dosing regimen. There were no cases of anaphylaxis in patients receiving placebo. Anaphylaxis generally occurred within 2 hours after treatment. Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to KRYSTEXXA or placebo injection with no other identifiable cause. Manifestations included wheezing, peri-oral or lingual edema, or hemodynamic instability, with or without rash or urticaria. Cases occurred in patients being pre-treated with one or more doses of an oral antihistamine, an intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of anaphylaxis and therefore the reported frequency may be an underestimate.

KRYSTEXXA should be administered in a healthcare setting by healthcare providers prepared to manage anaphylaxis. Patients should be pre-treated with antihistamines and corticosteroids. Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed type hypersensitivity reactions have also been reported. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA. Patients should be informed of the symptoms and signs of anaphylaxis and instructed to seek immediate medical care should anaphylaxis occur after discharge from the healthcare setting.

The risk of anaphylaxis is higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL. Because of the possibility that concomitant use of oral urate-lowering therapy and KRYSTEXXA may potentially blunt the rise of serum uric acid levels, it is recommended that before starting KRYSTEXXA patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

Infusion Reactions

During pre-marketing controlled clinical trials, infusion reactions were reported in 26% of patients treated with KRYSTEXXA 8 mg every 2 weeks, and 41% of patients treated with KRYSTEXXA 8 mg every 4 weeks, compared to 5% of patients treated with placebo. These infusion reactions occurred in patients being pre-treated with an oral antihistamine, intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of infusion reactions and therefore the reported frequency may be an underestimate.

Manifestations of these reactions included urticaria (frequency of 10.6%), dyspnea (frequency of 7.1%), chest discomfort (frequency of 9.5%), chest pain (frequency of 9.5%), erythema (frequency of 9.5%), and pruritus (frequency of 9.5%). These manifestations overlap with the symptoms of anaphylaxis, but in a given patient did not occur together to satisfy the clinical criteria for diagnosing anaphylaxis. Infusion reactions are thought to result from release of various mediators, such as cytokines. Infusion reactions occurred at any time during a course of treatment with approximately 3% occurring with the first infusion, and approximately 91% occurred during the time of infusion.

KRYSTEXXA should be administered in a healthcare setting by healthcare providers prepared to manage infusion reactions. Patients should be pre-treated with antihistamines and corticosteroids. KRYSTEXXA should be infused slowly over no less than 120 minutes. In the event of an infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate.

The risk of infusion reaction is higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL. Because of the possibility that concomitant use of oral urate-lowering therapy and KRYSTEXXA may potentially blunt the rise of serum uric acid levels, it is recommended that before starting KRYSTEXXA patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

G6PD Deficiency Associated Hemolysis and Methemoglobinemia

Life threatening hemolytic reactions and methemoglobinemia have been reported with KRYSTEXXA in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Because of the risk of hemolysis and methemoglobinemia, do not administer KRYSTEXXA to patients with G6PD deficiency [see Contraindications]. Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. For example, patients of African, Mediterranean (including Southern European and Middle Eastern), and Southern Asian ancestry are at increased risk for G6PD deficiency.

Gout Flares

During the controlled treatment period with KRYSTEXXA or placebo, the frequencies of gout flares were high in all treatment groups, but more so with KRYSTEXXA treatment during the first 3 months of treatment, and decreased in the subsequent 3 months of treatment. The percentages of patients with any flare for the first 3 months were 74%, 81%, and 51%, for KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. The percentages of patients with any flare for the subsequent 3 months were 41%, 57%, and 67%, for KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. Patients received gout flare prophylaxis with colchicine and/or nonsteroidal anti-inflammatory drugs (NSAIDs) starting at least one week before receiving KRYSTEXXA.

Gout flares may occur after initiation of KRYSTEXXA. An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Gout flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended starting at least 1 week before initiation of KRYSTEXXA therapy and lasting at least 6 months, unless medically contraindicated or not tolerated. KRYSTEXXA does not need to be discontinued because of a gout flare. The gout flare should be managed concurrently as appropriate for the individual patient.

Congestive Heart Failure

KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the clinical trials experienced exacerbation. Two cases of congestive heart failure exacerbation occurred during the trials in patients receiving treatment with KRYSTEXXA 8 mg every 2 weeks. No cases were reported in placebo-treated patients. Four subjects had exacerbations of pre-existing congestive heart failure while receiving KRYSTEXXA 8 mg every 2 weeks during the open-label extension study. Exercise caution when using KRYSTEXXA in patients who have congestive heart failure and monitor patients closely following infusion.

Re-treatment with KRYSTEXXA

No controlled trial data are available on the safety and efficacy of re-treatment with KRYSTEXXA after stopping treatment for longer than 4 weeks. Due to the immunogenicity of KRYSTEXXA, patients receiving re-treatment may be at increased risk of anaphylaxis and infusion reactions. Therefore, patients receiving re-treatment after a drug-free interval should be monitored carefully.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Anaphylaxis [see Warnings and Precautions]
- Infusion Reactions [see Warnings and Precautions]
- G6PD Deficiency Associated Hemolysis and Methemoglobinemia [see Warnings and Precautions]
- Gout Flares [see Warnings and Precautions]
- Congestive Heart Failure [see Warnings and Precautions]

Clinical Trials Experience

The data described below reflect exposure to KRYSTEXXA in patients with chronic gout refractory to conventional therapy in two replicate randomized, placebo-controlled, double-blind 6-month clinical trials: 85 patients were treated with KRYSTEXXA 8 mg every 2 weeks; 84 patients were treated with KRYSTEXXA 8 mg every 4 weeks; and 43 patients were treated with placebo.

Because clinical studies are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug, and may not predict the rates observed in a broader patient population in clinical practice.

The most common adverse reactions that occurred in ≥5% of patients treated with KRYSTEXXA 8 mg every 2 weeks are provided in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with KRYSTEXXA Compared to Placebo

Adverse Reaction (Preferred Term)	KRYSTEXXA 8 mg every 2 weeks (N=85) N[a] (%)	Placebo (N=43) N (%)
Gout flare	65 (77%)	35 (81%)
Infusion reaction	22 (26%)	2 (5%)
Nausea	10 (12%)	1 (2%)
Contusion[b] or Ecchymosis[b]	9 (11%)	2 (5%)
Nasopharyngitis	6 (7%)	1 (2%)
Constipation	5 (6%)	2 (5%)
Chest Pain	5 (6%)	1 (2%)
Anaphylaxis	4 (5%)	0 (0%)
Vomiting	4 (5%)	1 (2%)

[a] If the same subject in a given group had more than one occurrence in the same preferred term event category, the subject was counted only once.

[b] Most did not occur on the day of infusion and could be related to other factors (e.g., concomitant medications relevant to contusion or ecchymosis, insulin dependent diabetes mellitus).

Immunogenicity

Anti-pegloticase antibodies developed in 92% of patients treated with KRYSTEXXA every 2 weeks, and 28% for placebo. Anti-PEG antibodies were also detected in 42% of patients treated with KRYSTEXXA. High anti-pegloticase antibody titer was associated with a failure to maintain pegloticase-induced normalization of uric acid. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

There was a higher incidence of infusion reactions in patients with high anti-pegloticase antibody titer: 53% (16 of 30) in the KRYSTEXXA every 2 weeks group compared to 6% in patients who had undetectable or low antibody titers.

As with all therapeutic proteins, there is a potential for immunogenicity. The observed incidence of antibody positivity in an assay is highly dependent on several factors including assay sensitivity and specificity and assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the comparison of the incidence of antibodies to pegloticase with the incidence of antibodies to other products may be misleading.

Postmarketing Experience

General disorders and administration site conditions: asthenia, malaise, peripheral swelling have been identified during postapproval use of KRYSTEXXA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies of KRYSTEXXA in pregnant women. Based on animal reproduction studies, no structural abnormalities were observed when pegloticase was administered by subcutaneous injection to pregnant rats and rabbits during the period of organogenesis at doses up to 50 and 75 times, respectively, the maximum recommended human dose (MRHD). Decreases in mean fetal and pup body weights were observed at approximately 50 and 75 times the MRHD, respectively.

All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinical recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In 2 separate embryo-fetal developmental studies, pregnant rats and rabbits received pegloticase during the period of organogenesis at doses up to approximately 50 and 75 times the maximum recommended human dose (MRHD), respectively (on a mg/m2 basis at maternal doses up to 40 and 30 mg/kg twice weekly, in rats and rabbits, respectively). No evidence of structural abnormalities was observed in rats or rabbits. However, decreases in mean fetal and pup body weights were observed at approximately 50 and 75 times the MRHD in rats and rabbits, respectively (on a mg/m2 basis at maternal doses up to 40 and 30 mg/kg every other day, in rats and rabbits, respectively). No effects on mean fetal body weights were observed at approximately 10 and 25 times the MRHD in rats and rabbits, respectively (on a mg/m2 basis at maternal doses up to 10 mg/kg twice weekly in both species).

Lactation

Risk Summary

It is not known whether this drug is excreted in human milk. Therefore, KRYSTEXXA should not be used when breastfeeding unless the clear benefit to the mother can overcome the unknown risk to the newborn/infant.

Pediatric Use

The safety and effectiveness of KRYSTEXXA in pediatric patients less than 18 years of age have not been established.

Geriatric Use

Of the total number of patients treated with KRYSTEXXA 8 mg every 2 weeks in the controlled studies, 34% (29 of 85) were 65 years of age and older and 12% (10 of 85) were 75 years of age and older. No overall differences in safety or effectiveness were observed between older and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dose adjustment is needed for patients 65 years of age and older.

Renal Impairment

No dose adjustment is required for patients with renal impairment. A total of 32% (27 of 85) of patients treated with KRYSTEXXA 8 mg every 2 weeks had a creatinine clearance of ≤62.5 mL/min. No overall differences in efficacy were observed.

OVERDOSAGE

No reports of overdosage with KRYSTEXXA have been reported. The maximum dose that has been administered as a single intravenous dose is 12 mg as uricase protein. Patients suspected of receiving an overdose should be monitored, and general supportive measures should be initiated as no specific antidote has been identified.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

General Information

Provide and instruct patients to read the accompanying Medication Guide before starting treatment and before each subsequent treatment.

Anaphylaxis and Infusion Reactions

- Anaphylaxis and infusion reactions can occur at any infusion while on therapy. Counsel patients on the importance of adhering to any prescribed medications to help prevent or lessen the severity of these reactions.
- Educate patients on the signs and symptoms of anaphylaxis, including wheezing, peri-oral or lingual edema, hemodynamic instability, and rash or urticaria.
- Educate patients on the most common signs and symptoms of an infusion reaction, including urticaria (skin rash), erythema (redness of the skin), dyspnea (difficulty breathing), flushing, chest discomfort, chest pain, and rash.
- Advise patients to seek medical care immediately if they experience any symptoms of an allergic reaction during or at any time after the infusion of KRYSTEXXA.
- Advise patients to discontinue any oral urate-lowering agents before starting on KRYSTEXXA and not to take any oral urate-lowering agents while on KRYSTEXXA.

Glucose-6-phosphate dehydrogenase (G6PD) Deficiency

Inform patients not to take KRYSTEXXA if they have a condition known as G6PD deficiency. Explain to patients that G6PD deficiency is more frequently found in individuals of African, Mediterranean, or Southern Asian ancestry and that they may be tested to determine if they have G6PD deficiency, unless already known.

Gout Flares

Explain to patients that gout flares may initially increase when starting treatment with KRYSTEXXA, and that medications to help reduce flares may need to be taken regularly for the first few months after KRYSTEXXA is started. Advise patients that they should not stop KRYSTEXXA therapy if they have a flare.

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Prevention

Continued from cover

Burrows and her co-authors attributed the SDPI with helping to slow rates of ESKD among American Indian and Alaska Native people, suggesting the program's population-based approach may be a model for helping to stem rising ESKD rates (Table 1). "The Special Diabetes Program for Indians made access to quality diabetes care and treatment a reality for the communities it served," said Yvette Roubideaux, MD, MPH, director of the Policy Research Center at the National Congress of American Indians.

Community directed

The SDPI was created by Congress in 1997 (2) and provided dedicated funding for implementing best practices for diabetes prevention and treatment in more than 300 American Indian and Alaska Native communities in 35 states. A nationwide health system comprised of the IHS and tribal and urban Indian programs implements the program, Roubideaux explained. "This unique approach could only happen successfully if the local tribal nations and community members had a leading role in these activities," she explained.

The national Tribal Leaders Diabetes Committee, which has representation from each IHS area, helps set the formula for distributing funds to ensure all communities benefit and helps monitor the program's outcomes and advises the IHS on implementation. Local leaders and communities choose which strategies to implement, both inside and outside the clinic, based on local needs and priorities, Roubideaux said. The program helped cut diabetes-related ESKD among American Indian and Alaska Native adults in half, from 57.3 per 100,000 adults to 26.5 per 100,000 adults between 1996 and 2013, according to a previous CDC report (3). This decrease saved Medicare as much as $510 million over a decade (4).

The SDPI disseminated basic evidence-based diabetes prevention and care and basic CKD care to the entire primary care team, including physicians, dieticians, nurses, and pharmacists, explained Andrew Narva, MD, previous director of the National Kidney Disease Education Program and the Kidney Disease Program at the IHS. Narva, who is now retired and a doctoral student at the University of the District of Columbia, explained that the IHS disseminated the information through workshops, newsletters, and other vehicles to help make the entire team more comfortable in caring for patients with kidney diseases. One example of information sharing is training for dieticians on the best advice for patients with CKD. "It's the relentless implementation of simple, evidence-based care," Narva said.

Stephanie Mahooty, DNP, who worked alongside Narva as a registered nurse and renal case manager at IHS, said that the program emphasized checking patients' kidney function and helping to identify early patients at risk of progression of kidney diseases. The standards of care implemented as part of the SDPI (5) also helped ensure that those at-risk patients received appropriate care, such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. "The Special Diabetes Program implemented standards of care for diabetes and the CKD that made a dramatic improvement," Mahooty said. She said she was happy that the IHS updated the guidelines to include sodium glucose co-transporter 2 (SGLT2) inhibitors, which improve diabetes control, reduce the risk of cardiac death, and help reduce progression of kidney diseases. Narva agreed that the SGLT2 inhibitors could be a "game-changer."

Clinician and community partnerships are also vital to addressing the many factors that may contribute to increased risk of diabetes in American Indian and Alaska Native communities or hamper prevention efforts. "Clinicians must understand that the care they provide in the clinic is only a part of the solution since there are so many social determinants in communities that can either support or hinder diabetes treatment and prevention efforts," Roubideaux explained. For example, in Juneau, Owen and her colleagues recognized that many patients did not have access to transportation, so they provided it. Many patients also relied on foods they harvested themselves, so she and her colleagues emphasized the benefits of those traditional foods, the exercise required to gather them, and the communal nature of harvests.

To aid this kind of collaboration, the SDPI also funds community-based activities to promote diabetes education, awareness, and behavior change, noted Roubideaux. Some communities have incorporated their local culture and language into the program, she added. For example, the activities may include recipes and cooking classes that use local foods with reduced fat, that portion sizes or promote traditional sports, or that provide lessons about how to grow healthier foods, including foods that have long been important to their communities. "All of these strategies made learning how to prevent and treat diabetes more interesting and relevant to community members, which likely led to more participation and success," Roubideaux said. Inviting families to join activities, such as prediabetes education programming, community meals, and events like community diabetes walks, also helped improve overall community well-being, noted Owen. She added, "The people who participated in the program loved it, and their families benefited from it, too."

A model for change

Implementing the indigenous ideas that make up the foundation of the SDPI program, such as the emphasis on community health and monitoring and adjusting to community needs, may offer benefits for other communities as well, said Owen. "Indigenous ways have a lot of benefits, not just for native people but for all people," she said.

One of the lessons of the SDPI, Roubideaux said, is that chronic diseases, such as diabetes, require a community-wide approach to prevention and treatment, along with tailored strategies that are responsive to local cultures, traditions, and circumstances. But doing this takes a commitment to both funding and staffing. "The Special Diabetes Program for Indians revealed that change is possible if sufficient resources and support are available in the context of allowing communities to lead those changes," Roubideaux said

Educating clinicians about diabetes and kidney diseases and emphasizing team-based care are also crucial, said Mahooty, now a nurse practitioner in private practice in Albuquerque, New Mexico. Mahooty said she uses the SDPI standards of care and educational materials to train new colleagues. She also continues to apply the team-based approach to coordinate patients' care with their primary care physicians, pharmacists, and other care providers. For example, she talked to a patient's primary care clinician about starting the patient on an SGLT2 and helped explain to the patient the benefit of the medication. "Collaboration is very important," she said.

Burrows, who left the CDC shortly after the interview, also emphasized the importance of population health and team-based approaches that include testing for kidney diseases and case management. "Continued efforts to deliver interventions that improve care and management of ESKD risk factors among persons with diabetes and hypertension might slow the increase and eventually reverse the trend in incident ESKD cases, not only for American Indian or Alaska Native populations but for all populations at risk of developing ESKD," she said.

Continued investment in the SDPI, which was last reauthorized in December 2020 for 3 years (6), is also essential to helping to preserve and expand the positive impact of the program in indigenous communities. "The Special Diabetes Program for Indians has resulted in positive outcomes that many thought were not possible, but since diabetes is a chronic disease, the services and support provided by this program would not be possible without continued funding for these programs," Roubideaux concluded. ■

Table 1. The power of population health

The use of population health and team-based approaches to diabetes and kidney care is recommended to help cut rising ESKD rates in the United States. Suggestions from the CDC (7) for implementing these concepts include the following:

- **Use population health approaches to diabetes care. Assess long-term outcomes, and address disparities. Promote wellness of the entire community, and connect people to local resources, including healthy food, transportation, housing, and mental health care.**
- **Develop a coordinated team approach to diabetes care. Team-based care can include patient education, community outreach, care coordination, tracking of health outcomes, and access to health care providers, nutritionists, diabetes educators, pharmacists, community health workers, and behavioral health clinicians.**
- **Integrate prevention and education of kidney diseases into routine diabetes care. Screen people with diabetes for kidney diseases, and make sure that kidney diseases are routinely addressed as part of diabetes care.**

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Donor DNA

Continued from cover

tive value of 77.5% for graft injury with a negative predictive value of 71.6%.

Clinical trials have shown that routine dd-cfDNA monitoring can detect allograft injury after solid organ transplantation, as well as assess the response to therapy, including anti-rejection therapy. This study validates the effectiveness of dd-cfDNA in identifying clinical and subclinical kidney allograft rejection in a real-world clinical setting. The authors state: "[P]ersistently low dd-cfDNA levels may accurately identify allograft quiescence or absence of injury, paving the way for personalization of immunosuppression trials" [Bu L, et al. Clinical outcomes from the Assessing Donor-Derived Cell-Free DNA Monitoring Insights of Kidney Allografts with Longitudinal Surveillance (ADMIRAL) study. *Kidney Int* 2022; 101:793–803. doi: 10.1016/j.kint.2021.11.034].■

Essential versus Necessary: The Ongoing Story of Physician Burnout

By Charuhas V. Thakar

The effort conundrum

Let me dive right in! A traditional business plan equates one full-time equivalent (FTE) to 8 out of 10 half-day sessions of direct clinical work, which expects the physician to complete an average of 12 patient visits in a 4-hour clinic session (a typical visit is 15 minutes for follow-up and 30 minutes for a new patient). There are three recipients of the deliverables during a clinic visit: 1) the recipient of the clinical care is the patient; 2) the recipient of the professional billing is the practice plan; and 3) the recipient of most of the work on electronic medical records is the health system/compliance. Clinicians are provided 1 full day to "catch up" on all of these three deliverables, yet each of these three deliverables is expected to occur within 24–48 hours of the visit to avoid disruption in clinical care or face system penalties. Implicit in this model is cannibalization of at least an additional 20% of personal time but without any effort or monetary credit for it.

There is a popular workaround across most academic institutions in the country, whereby the work hours per week are extended to 55–60 hours, which does not include on-call hours when taking calls from home. This workaround is made to "fit" the physician effort in an appropriate "spreadsheet box" in the annual departmental budgets. First of all, this hides the fact that most physicians actually work more than one FTE. More importantly, this effort only accounts for direct patient care time and excludes care coordination and electronic health record charting. The metrics of effort reporting are woefully incongruent with the actual effort needed to achieve the task, and for physicians and advanced practitioners, that "task" is delivering compassionate, high-quality, and safe patient care. Compassionate, high-quality, and safe patient care: These buzzwords are easy to write in a business plan or a vision statement, but somehow, we seem to have lost ourselves in translation. We are making the deliverer of this care an invisible entity: the clinician, the provider.

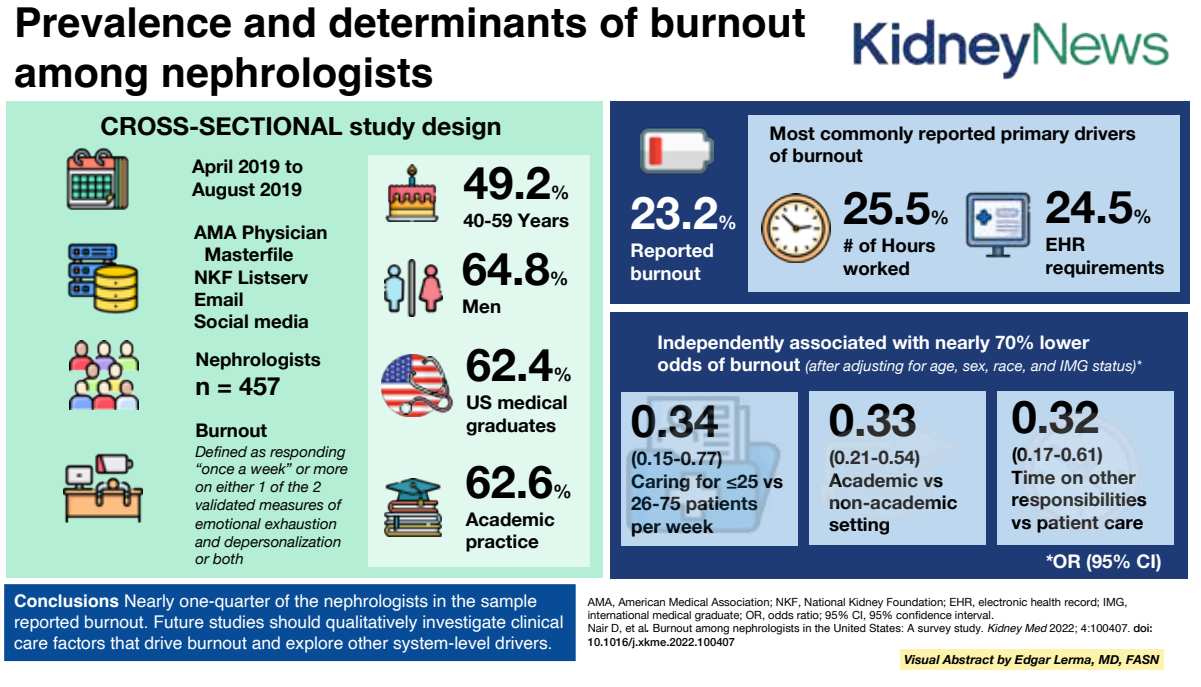
A majority of nephrologists serve in community-based practices and face yet another unique reality. We are probably among the few remaining, if not the only, subspecialties that still operate as "group practices," which are not part of large, consolidated health care delivery systems. This leads to a syndrome of being "institutionally orphaned." An average nephrologist will round at two to three hospitals to deliver inpatient care, likely across multiple health systems. This will entail different medical staff rules, electronic records, and compliance requirements. In addition, nephrologists will have their own office practice, for which they are responsible for managing. And finally, we deliver dialysis care, in which an average nephrologist spends at least half of a day per week driving between dialysis facilities. Additionally, there is the interface with dialysis corporations, which comes with its own advantages and disadvantages. It is our relationship with dialysis corporations that allows us to be fiscally sustainable and not be forced to be part of consolidated health systems, but that comes at a price of being stretched in multiple directions.

The fiscal conundrum

Medicare spends, on average, $100,000 per dialysis patient per year. Approximately 60% of this expenditure translates as a revenue source to hospitals. Less than 20% of this expenditure formulates as physician fee-for-service revenue (1). It is mathematically impossible to sustain a nephrology practice simply relying on professional fees. New payment models are crafted to save Medicare expenditures and reinvest part of those savings toward the providers. However, these models have a finite ceiling. Thus, it is essential that downstream revenues generated by hospitals and health care systems need to be reinvested across all disciplines. Without doing so, we will eventually erode the ability to deliver high-quality care to this complex subgroup of patients.

This paradigm of care delivery is simply not sustainable. It is almost guaranteed that we will face burnout and compassion fatigue—some of us sooner rather than later. In a recent *Kidney Medicine* article by Dr. Devika Nair and colleagues (2), they surveyed a large sample of nephrology providers to assess causes and impact of physician burnout. An astounding one in four physicians reported burnout. The primary drivers included electronic records and hours of work. The reported value of these factors far outweighed the monetary concerns.

The lines between essential and necessary have grown increasingly fuzzy, particularly over the last 24 months. Health care systems, academic institutions, and dialysis corporations need to wake up or need to be woken up to address this existential threat. The current path makes nephrology an "endangered discipline," which will continue to face workforce challenges unless there are substantive core fixes. Moreover, while facing burnout ourselves, it is challenging to inspire our trainees; thus, we may compound the effect in terms of career interest in our discipline. We will be ignoring this physician burnout at our own peril and to the detriment of serving our valuable and vulnerable patients. ■



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There's more than one reason why Parsabiv® is used by dialysis care teams for their clinically appropriate patients.

Indication

Parsabiv® (etelcalcetide) is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Limitations of Use:

Parsabiv® has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with CKD who are not on hemodialysis and is not recommended for use in these populations.

Important Safety Information for Parsabiv®

Contraindication: Parsabiv® is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including face edema and anaphylactic reaction, have occurred.

Hypocalcemia: Parsabiv® lowers serum calcium and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause QT interval prolongation and ventricular arrhythmia. Patients with conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to Parsabiv®. Closely monitor corrected serum calcium and QT interval in patients at risk on Parsabiv®.

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to Parsabiv®. Monitor corrected serum calcium in patients with seizure disorders on Parsabiv®.

Concurrent administration of Parsabiv® with another oral calcimimetic could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to Parsabiv® should discontinue cinacalcet for at least 7 days prior to initiating Parsabiv®. Closely monitor corrected serum calcium in patients receiving Parsabiv® and concomitant therapies known to lower serum calcium.

Measure corrected serum calcium prior to initiation of Parsabiv®. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with Parsabiv®. Measure PTH 4 weeks after initiation or dose adjustment of Parsabiv®. Once the maintenance dose has been established, measure PTH per clinical practice.

Worsening Heart Failure: In Parsabiv® clinical studies, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. Closely monitor patients treated with Parsabiv® for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding: In clinical studies, 2 patients treated with Parsabiv® in 1253 patient years of exposure had upper gastrointestinal (GI) bleeding at the time of death. The exact cause of GI bleeding in these patients is unknown and there were too few cases to determine whether these cases were related to Parsabiv®.

Patients with risk factors for upper GI bleeding, such as known gastritis, esophagitis, ulcers or severe vomiting, may be at increased risk for GI bleeding with Parsabiv®. Monitor patients for worsening of common Parsabiv® GI adverse reactions and for signs and symptoms of GI bleeding and ulcerations during Parsabiv® therapy.

Adynamic Bone: Adynamic bone may develop if PTH levels are chronically suppressed.

Adverse Reactions: In clinical trials of patients with secondary HPT comparing Parsabiv® to placebo, the most common adverse reactions were blood calcium decreased (64% vs. 10%), muscle spasms (12% vs. 7%), diarrhea (11% vs. 9%), nausea (11% vs. 6%), vomiting (9% vs. 5%), headache (8% vs. 6%), hypocalcemia (7% vs. 0.2%), and paresthesia (6% vs. 1%).

Please see Brief Summary of full Prescribing Information on adjacent page.

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Parsabiv®
(etelcalcetide) Injection for intravenous use
2.5mg/0.5mL | 5mg/1mL | 10mg/2mL

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Parsabiv®
(etelcalcetide) Injection for intravenous use

2.5mg/0.5mL | 5mg/1mL | 10mg/2mL

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

PARSABIV is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Limitations of Use:

PARSABIV has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with chronic kidney disease who are not on hemodialysis and is not recommended for use in these populations.

CONTRAINDICATIONS

Hypersensitivity

PARSABIV is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including face edema and anaphylactic reaction, have occurred with PARSABIV *[see Adverse Reactions (6) in PARSABIV full prescribing information]*.

WARNINGS AND PRECAUTIONS

Hypocalcemia

PARSABIV lowers serum calcium *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]* and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause paresthesias, myalgias, muscle spasms, seizures, QT interval prolongation, and ventricular arrhythmia.

QT Interval Prolongation and Ventricular Arrhythmia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). In these studies, the incidence of a maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]*. Patients with congenital long QT syndrome, history of QT interval prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to PARSABIV. Closely monitor corrected serum calcium and QT interval in patients at risk receiving PARSABIV.

Seizures

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to PARSABIV. Monitor corrected serum calcium in patients with seizure disorders receiving PARSABIV.

Risk of Hypocalcemia with Other Serum Calcium Lowering Products

Concurrent administration of PARSABIV with another oral calcium-sensing receptor agonist could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to PARSABIV should discontinue cinacalcet for at least 7 days prior to initiating PARSABIV *[see Dosage and Administration (2.4) in PARSABIV full prescribing information]*. Closely monitor corrected serum calcium in patients receiving PARSABIV and concomitant therapies known to lower serum calcium.

Monitoring Serum Calcium and Patient Education

Measure corrected serum calcium prior to initiation of PARSABIV. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with PARSABIV *[see Dosage and Administration (2.2) in PARSABIV full prescribing information]*. Educate patients on the symptoms of hypocalcemia and advise them to contact a healthcare provider if they occur.

Management of Hypocalcemia

If corrected serum calcium falls below the lower limit of normal or symptoms of hypocalcemia develop, start or increase calcium supplementation (including calcium, calcium-containing phosphate binders, and/or vitamin D sterols or increases in dialysate calcium concentration). PARSABIV dose reduction or discontinuation of PARSABIV may be necessary *[see Dosage and Administration (2.2) in PARSABIV full prescribing information]*.

Worsening Heart Failure

In clinical studies with PARSABIV, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. In clinical studies, heart failure requiring hospitalization occurred in 2% of PARSABIV-treated patients and 1% of placebo-treated patients. Reductions in corrected serum calcium may be associated with congestive heart failure, however, a causal relationship to PARSABIV could not be completely excluded. Closely monitor patients treated with PARSABIV for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding

In clinical studies, two patients treated with PARSABIV in 1253 patient-years of exposure had upper gastrointestinal (GI) bleeding noted at the time of death while no patient in the control groups in 384 patient-years of exposure had upper GI bleeding noted at the time of death. The exact cause of GI bleeding in these patients is unknown, and there were too few cases to determine whether these cases were related to PARSABIV.

Patients with risk factors for upper GI bleeding (such as known gastritis, esophagitis, ulcers, or severe vomiting) may be at increased risk for GI bleeding while receiving PARSABIV treatment. Monitor patients for worsening of common GI adverse reactions of nausea and vomiting associated with PARSABIV *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]* and for signs and symptoms of GI bleeding and ulcerations during PARSABIV therapy. Promptly evaluate and treat any suspected GI bleeding.

Adynamic Bone

Adynamic bone may develop if PTH levels are chronically suppressed. If PTH levels decrease below the recommended target range, the dose of vitamin D sterols and/or PARSABIV should be reduced or therapy discontinued. After discontinuation, resume therapy at a lower dose to maintain PTH levels in the target range *[see Dosage and Administration (2.1) in PARSABIV full prescribing information]*.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Hypocalcemia *[see Warnings and Precautions (5.1) in PARSABIV full prescribing information]*
- Worsening Heart Failure *[see Warnings and Precautions (5.2) in PARSABIV full prescribing information]*
- Upper Gastrointestinal Bleeding *[see Warnings and Precautions (5.3) in PARSABIV full prescribing information]*
- Adynamic Bone *[see Warnings and Precautions (5.4) in PARSABIV full prescribing information]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data in Table 2 are derived from two placebo-controlled clinical studies in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis. The data reflect exposure of 503 patients to PARSABIV with a mean duration of exposure to PARSABIV of 23.6 weeks. The mean age of patients was approximately 58 years, and 60% of the patients were male. Of the total patients, 67% were Caucasian, 28% were Black or African American, 2.6% were Asian, 1.2% were Native Hawaiian or Other Pacific Islander, and 1.6% were categorized as Other.

Table 2 shows common adverse reactions associated with the use of PARSABIV in the pool of placebo-controlled studies. These adverse reactions occurred more commonly on PARSABIV than on placebo and were reported in at least 5% of patients treated with PARSABIV.

Table 2: Adverse Reactions Reported in ≥ 5% of PARSABIV-Treated Patients

Adverse Reaction*	Placebo (N = 513)	PARSABIV (N = 503)
Blood calcium decreased[a]	10%	64%
Muscle spasms	7%	12%
Diarrhea	9%	11%
Nausea	6%	11%
Vomiting	5%	9%
Headache	6%	8%
Hypocalcemia[b]	0.2%	7%
Paresthesia[c]	1%	6%

*Included adverse reactions reported with at least 1% greater incidence in the PARSABIV group compared to the placebo group

[a] Asymptomatic reductions in calcium below 7.5 mg/dL or clinically significant asymptomatic reductions in corrected serum calcium between 7.5 and < 8.3 mg/dL (that required medical management)

[b] Symptomatic reductions in corrected serum calcium < 8.3 mg/dL

[c] Paresthesia includes preferred terms of paresthesia and hypoesthesia

Other adverse reactions associated with the use of PARSABIV but reported in < 5% of patients in the PARSABIV group in the two placebo-controlled clinical studies were:

- Hyperkalemia: 3% and 4% for placebo and PARSABIV, respectively.
- Hospitalization for Heart Failure: 1% and 2% for placebo and PARSABIV, respectively.
- Myalgia: 0.2% and 2% for placebo and PARSABIV, respectively.
- Hypophosphatemia: 0.2% and 1% for placebo and PARSABIV, respectively.

Description of Selected Adverse Reactions

Hypocalcemia

In the combined placebo-controlled studies, a higher proportion of patients on PARSABIV developed at least one corrected serum calcium value below 7.0 mg/dL (7.6% PARSABIV, 3.1% placebo), below 7.5 mg/dL (27% PARSABIV, 5.5% placebo), and below 8.3 mg/dL (79% PARSABIV, 19% placebo). In the combined placebo-controlled studies, 1% of patients in the PARSABIV group and 0% of patients in the placebo group discontinued treatment due to an adverse reaction attributed to a low corrected serum calcium.

Hypophosphatemia

In the combined placebo-controlled studies, 18% of patients treated with PARSABIV and 8.2% of patients treated with placebo had at least one measured phosphorus level below the lower normal limit (i.e., 2.2 mg/dL).

QTc Interval Prolongation Secondary to Hypocalcemia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). The patient incidence of maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively.

Hypersensitivity

In the combined placebo-controlled studies, the subject incidence of adverse reactions potentially related to hypersensitivity was 4.4% in the PARSABIV group and 3.7% in the placebo group. Hypersensitivity reactions in the PARSABIV group were pruritic rash, urticaria, and face edema.

Immunogenicity

As with all peptide therapeutics, there is potential for immunogenicity. The detection of anti-drug binding antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to etelcalcetide with the incidence of antibodies to other products may be misleading.

In clinical studies, 7.1% (71 out of 995) of patients with secondary hyperparathyroidism treated with PARSABIV for up to 6 months tested positive for binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing anti-etelcalcetide antibodies.

No evidence of altered pharmacokinetic profile, clinical response, or safety profile was associated with pre-existing or developing anti-etelcalcetide antibodies.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on the use of PARSABIV in pregnant women. In animal reproduction studies, effects were seen at doses associated with maternal toxicity that included hypocalcemia. In a pre- and post-natal study in rats administered etelcalcetide during organogenesis through delivery and weaning, there was a slight increase in perinatal pup mortality, delay in parturition, and transient effects on pup growth at exposures 1.8 times the human exposure for the clinical dose of 15 mg three times per week. There was no effect on sexual maturation, neurobehavioral, or reproductive function in the rat offspring. In embryo-fetal studies, when rats and rabbits were administered etelcalcetide during organogenesis, reduced fetal growth was observed at exposures 2.7 and 7 times exposures for the clinical dose, respectively.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

There were no effects on embryo-fetal development in Sprague-Dawley rats when etelcalcetide was dosed at 0.75, 1.5, and 3 mg/kg/day by the intravenous route during organogenesis (pre-mating to gestation day 17) at exposures up to 1.8 times human exposures at the clinical dose of 15 mg three times per week based on AUC. No effects on embryo-fetal development were observed in New Zealand White rabbits at doses of etelcalcetide of 0.375, 0.75, and 1.5 mg/kg by the intravenous route (gestation day 7 to 19), representing up to 4.3 times human exposures based on AUC. In separate studies at higher doses of 4.5 mg/kg in rats (gestation days 6 to 17) and 2.25 mg/kg in rabbits (gestation days 7 to 20), representing 2.7- and 7-fold clinical exposures, respectively, there was reduced fetal growth associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption.

In a pre- and post-natal development study in Sprague-Dawley rats administered etelcalcetide at 0.75, 1.5, and 3 mg/kg/day by the intravenous route (gestation day 7 to lactation day 20), there was a slight increase in perinatal pup mortality, delay in parturition, and transient reductions in post-natal growth at 3 mg/kg/day (representing 1.8-fold human exposures at the clinical dose of 15 mg three times per week based on AUC), associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption. There were no effects on sexual maturation, neurobehavioral, or reproductive function at up to 3 mg/kg/day, representing exposures up to 1.8-fold human exposure based on AUC.

Lactation

Risk Summary

There are no data regarding the presence of PARSABIV in human milk or effects on the breastfed infant or on milk production. Studies in rats showed [^{14}C]-etelcalcetide was present in the milk at concentrations similar to plasma. Because of the potential for PARSABIV to cause adverse effects in breastfed infants including hypocalcemia, advise women that use of PARSABIV is not recommended while breastfeeding.

Data

Presence in milk was assessed following a single intravenous dose of [^{14}C]-etelcalcetide in lactating rats at maternal exposures similar to the exposure at the human clinical dose of 15 mg three times per week. [^{14}C]-etelcalcetide-derived radioactivity was present in milk at levels similar to plasma.

Pediatric Use

The safety and efficacy of PARSABIV have not been established in pediatric patients.

Geriatric Use

Of the 503 patients in placebo-controlled studies who received PARSABIV, 177 patients (35.2%) were ≥ 65 years old and 72 patients (14%) were ≥ 75 years old.

No clinically significant differences in safety or efficacy were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old). No differences in plasma concentrations of etelcalcetide were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old).

OVERDOSAGE

There is no clinical experience with PARSABIV overdosage. Overdosage of PARSABIV may lead to hypocalcemia with or without clinical symptoms and may require treatment. Although PARSABIV is cleared by dialysis, hemodialysis has not been studied as a treatment for PARSABIV overdosage. In the event of overdosage, corrected serum calcium should be checked and patients should be monitored for symptoms of hypocalcemia, and appropriate measures should be taken *[see Warnings and Precautions (5.1) in PARSABIV full prescribing information]*.

AMGEN®

PARSABIV® (etelcalcetide)

Manufactured for:
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Patent: http://pat.amgen.com/Parsabiv/

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ASN President's Update

Embracing Pride Month and Nephrology's Ongoing Inclusion

By Susan E. Quaggin

As we approach the middle of the year, those of us who live in locations with long, harsh winters are basking in the remainder of spring and its glorious diversity: multi-colored blossoms and greenery, rain, sun, and ever-changing temperatures. During my #850challenge (1) run this morning, I was struck how fitting it is that the joy of spring and oncoming summer coincides with Pride month—a month filled with opportunities to celebrate diversity and all the power and growth it brings to the kidney community.

Pride month is celebrated annually in June in the United States, culminating in festive and colorful parades—this year on June 28th—to commemorate the Stonewall riots in New York, NY, in 1969, which sparked the U.S. lesbian, gay, bisexual, transgender, queer (or sometimes questioning), and others (LGBTQ+) revolution. In other countries, Pride month is celebrated in October where it aligns with national coming out day on October 11 or at other times throughout the year.

Pride month also provides us an important opportunity to remember all that has been gained during the past 50 years and to recognize the critical importance and value LGBTQ+ communities bring to all aspects of our society (2). Although milestones (Table 1) show important advances in civil rights, we must acknowledge there is much more to do and explore where we risk losing ground.

As physicians and other members of the kidney care team, we took an oath when we entered the profession: We must ensure trainees, faculty, and experienced practitioners receive appropriate education to provide inclusive and affirming care for all members of LGBTQ+ communities, and we must have leaders and professionals who represent diverse populations across all aspects of society and our profession to realize health justice.

In the health community, patients—including those with kidney diseases—who identify as LGBTQ+ and/or as other sexual and gender minority (SGM) individuals face injustices in their everyday lives, including a disproportionate rate of kidney diseases compared with those who are not in LGBTQ+ communities (3). As outlined in an editorial by Mohottige and Lunn (4), non-discrimination policies across the United States exist in a patchwork manner and "do not universally prohibit discrimination based on sexual orientation and gender identity…in public accommodations, including in health care centers, such as dialysis facilities" (5). People who identify as SGMs may be discouraged from seeking medical care because of potential denial of care, job loss, and/or fear of discrimination and harassment. Within the health care system, individuals who are SGMs face an excess burden of suboptimal health care due to implicit and explicit bias (6). For some kidney care and treatment options, such as transplant and home dialysis, demonstration of a supportive home environment and care partners are needed. Without inclusive and affirming health care, some patients may not feel comfortable sharing their family situation with a care team.

Progress

What can we do within the kidney community? Nephrology is best when it leads from the front. It is time we stand up to disparities that face our colleagues and patients, as well as others in LGBTQ+ communities, and implement changes in education, increase awareness, and reexamine practices or lab tests that may cause harm.

Last year, the race modifier was removed from the kidney estimating formula and replaced by a new race-free formula. In the new chronic kidney disease-Epidemiology Collaboration (CKD-EPI) 2021 formula, the sex coefficient remains. It is tantamount that as kidney care professionals, we examine the role of the female sex coefficient in the context of our patients who are transgender and/or gender expansive and are reported to be at higher risk of acute kidney injury and CKD (7). The sex variable is binary and does not take into account the role of gender-affirming hormone therapies (e.g., estrogen and testosterone) that may impact muscle mass and creatinine production.

As we celebrate Pride month and consider Kidney Week, which will be held this year in Florida, November 3–6, it is impossible not to recognize the legislative actions in the United States that may reverse gains in civil rights and freedoms. Perhaps most frighteningly for patient care, the sanctity of the patient-physician relationship is threatened by proposed policies in a number of U.S. states. As kidney health professionals, we are bound by oath to do what is right for patients, always.

In 1987, during the early days of the HIV epidemic, I vividly remember a morning in late June. I was a clinical clerk (4th-year medical student) on the internal medicine service. In Toronto, internal medicine ward rounds were the focus every day, with an emphasis on clinical acumen. Each morning, the attending physician would round with the trainees. He/she/they would perform a history and physical examination on each patient and confirm or refute a trainee's findings and diagnosis. On this particular morning, we stopped by the room of a young man admitted with a provisional diagnosis of pneumocystis carinii pneumonia, the most common complication of HIV infection at that time. We discussed the patient's history before entering the room. As I stood and watched the attending physician, tradition was broken. Unlike with the three patients before this one, my attending did not shake the patient's hand, and he did not lay his stethoscope on the patient's chest. In fact, he did not lay his hands on the patient at all. I was bewildered by the behavior, and as we exited the room, the attending discussed HIV briefly, as well as lifestyle choices. To this day, I am overcome by emotion—with anger and heartbreak—when I remember this encounter, because I had realized for the first time that not all MDs are physicians or healers.

The following year, I rotated on the benign hematology service, which was run by a chief with a formidable reputation. She had studied at the National Institutes of Health in the 1970s, which was unprecedented in those days for women. She was known for her incredibly high expectations of trainees. Throughout the 2 months I spent on this service, I came to view her as a role model and as a physician whose approach to patients I would aspire to throughout my career. She was instrumental in supporting the launch of Casey House, a caring and equitable hospice for patients living with AIDS in Toronto.

The discrimination that marked the early days of the HIV epidemic was fueled by fear and hatred. We cannot step backward. Earlier this month, I shared a letter (8) with the membership regarding the ASN Council's decision to hold Kidney Week in Orlando, FL, this fall, as well as a series of action steps to demonstrate our unwavering support for LGBTQ+ communities (Table 2). Since I sent the letter, I have received feedback from ASN members and other stakeholders. Most comments have strongly supported the council's decision, plan, and perspective. However, importantly, several colleagues and friends have urged caution. They are understandably concerned about ASN taking a political position. We all know that sometimes politics and medicine collide. ASN, other specialty societies, and health leaders worldwide will be judged on how they navigate our increasingly difficult, acrimonious, and uncertain world. As ASN president, my North Star is always asking, "What is best for patients and for people living with kidney diseases?"

This iridescent spring season should remind us of the transformation occurring in nephrology through innovation—a transformation that will never be fully realized without full inclusion. As we celebrate Pride month, let us remember who we are and what we can accomplish when we stand united (9). Let us remember we are stronger when we build solutions that incorporate perspectives from all professionals and patients.

Table 1. Examples of LGBTQ+ progress in the United States since 1969

Decade	Milestone
1970s	The American Psychiatric Association "removes homosexuality from its list of mental disorders."
1980s	Wisconsin becomes first state "to outlaw discrimination based on sexual orientation."
1990s	The Hate Crimes Sentencing Enhancement Act goes into effect, allowing judges "to impose harsher sentences if there is evidence showing that a victim was selected because of the 'actual or perceived race, color, religion, national origin, ethnicity, gender, disability, or sexual orientation of any person.'"
2000s	The U.S. Supreme Court "strikes down the 'homosexual conduct' law, which decriminalizes same-sex sexual conduct," and the "first legal same-sex marriage in the United States takes place in Massachusetts."
2010s	"'Don't Ask, Don't Tell' is repealed, ending a ban on gay men and lesbians from serving openly in the military," and the Military Equal Opportunity policy is "adjusted to include gay and lesbian military members."
2020s	The U.S. Supreme Court "rules that federal law protects LGBTQ workers from discrimination," and the Senate confirms the first "openly gay Cabinet member" (current U.S. Secretary of Transportation Pete Buttigieg) and "the first out transgender federal official" (current Department of Health and Human Services Assistant Secretary for Health Admiral Rachel L. Levine, MD)

Reprinted from Cable News Network (2).

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Table 2. ASN will bring its values to Florida

Making a significant contribution to the onePULSE Foundation (10) in support of LGBTQ+ communities and sharing information about other worthwhile causes for participants to support in Orlando
Supporting at-risk businesses in Orlando, including LGBTQ+-owned restaurants
Working with local media outlets to raise awareness of kidney diseases in Florida and voicing our opposition to the "Don't Say Gay" bill and other discriminatory practices
Promoting ASN's commitment to eliminate disparities based on sexual identity, gender, race, or ethnicity throughout the meeting (such as the annual Wesson-Himmelfarb Diversity and Inclusion Lunch and the annual LGBTQ+ and Allies Reception)
Providing educational sessions focused on transgender kidney health and equity issues (For the first time this year, Kidney Week will include a "health equity" abstract category.)
Celebrating our transgender kidney heroes and allies who are transforming care through their commitment to innovation

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Climate Health Is Kidney Health

This is an abridged version of ASN's Statement on Climate Change, which can be viewed in its entirety online at www.asn-online.org.

The American Society of Nephrology (ASN) calls on kidney health professionals to take action to address the impact of climate change on the 850 million people—including more than 37 million Americans—living with kidney diseases across the world who are uniquely vulnerable to the effects of climate change.

Climate change—defined by the United Nations Framework Convention on Climate Change as "a change of climate which is attributed directly or indirectly to human activity that alters the composition of the global atmosphere and which is in addition to natural climate variability observed over comparable periods of time"—poses an existential crisis that threatens the viability of life on this planet. Projections by the Intergovernmental Panel on Climate Change show global surface temperatures are likely to increase by 2.0° Celsius by mid-century if emissions remain at current levels and by as much as 3.5° Celsius by the end of the century. If emissions continue to increase, global surface temperatures are likely to increase by as much as 5.7° Celsius.

The effects of climate change (heat waves, precipitation events, droughts, and cyclone activity) are expected to become more extreme and occur with greater frequency. Specifically, extreme weather patterns may lead to climate events, such as floods and droughts; a reduction in agriculture and food security; or a decrease in water supply and quality due to increases in temperature and changes in precipitation. The diverse detrimental effects of climate change are compounded for people with kidney diseases, as this population is both more susceptible to the direct health impacts of climate change and vulnerable to breakdowns in the health care infrastructure during natural disasters.

Multiple cardinal features of climate change directly impact kidney health. First, heat exposure and dehydration have been implicated in epidemics of chronic kidney failure in Latin America and elsewhere (i.e., Mesoamerican nephropathy) and are also risk factors for kidney stones and acute kidney injury. Second, poor air quality has been linked to progressive chronic kidney failure. Vector-borne illnesses remain important causes of kidney diseases in developing countries and are becoming more prevalent across the world, including in developed countries and previously inhospitable climates, due to changes in temperature, precipitation modification of the landscape, and human behavior that increases vector-human contact. Finally, given that people with kidney diseases tend to have multiple other chronic conditions, such as heart and lung disease, and are prone to infection, the impact of climate change is likely to disproportionately impact this population.

More than 500,000 Americans with kidney failure require daily or thrice-weekly dialysis treatments to live, and the majority of these people receive thrice-weekly hemodialysis treatments in an outpatient dialysis center. Disruption of medical infrastructure and access to a medically pure water supply, necessary for dialysis during a natural disaster, can be immediately life threatening for this population.

More broadly, the population of people with kidney diseases is disproportionately composed of people at socioeconomic disadvantage who are also bearing the greatest burden of climate change. Kidney diseases are associated with social determinants of health and are even concentrated in geographic "hotspots," such as industrial farming areas, which are especially impacted by climate change. Furthermore, kidney diseases may be associated with occupations that involve extended exposure to extreme temperatures and an increasingly hostile outdoor environment, such as agricultural labor, which are disproportionately held by people with lower socioeconomic status. The confluence of socioeconomic, geographic, and climate change risk factors may increase the incidence of kidney diseases and disrupt access to care.

Kidney health professionals must acknowledge that the health care industry is a significant contributor to greenhouse gas emissions and climate change. It is estimated that the delivery of health care accounts for up to 5% of annual global greenhouse gas emissions, and the management of kidney diseases contributes disproportionately to the overall environmental footprint of the health care industry due to the resource intensiveness of kidney replacement therapies. Hemodialysis, in particular, is an extremely water- and power-hungry therapy, consuming approximately 156 billion liters of water and 1.62 billion kW/hour of power in the treatment of about 2 million people per year. It also generates excessive amounts of plastic waste—approximately 625,000 tons per year—most of which is produced and discarded in an environmentally damaging manner.

Climate change threatens to increase the incidence and prevalence of kidney diseases, disrupt access to care, and widen inequity in kidney health. The more than 21,000 kidney health professionals who comprise the American Society of Nephrology are dedicated to creating a world without kidney diseases. ASN believes that climate health is kidney health and calls on kidney health professionals across the globe to:

- Support people with kidney diseases to survive climate change by:
  - Researching the biological and population-level impacts of climate change on kidney health and developing interventions to mitigate these impacts
  - Fostering community resilience to the impacts of climate change, including disaster preparedness focused on kidney health care systems for extreme weather events
  - Broadening access to, and the supply chain for, existing therapies, such as home dialysis and transplantation, and developing new therapies, such as wearable or implantable artificial kidneys, which increase patient mobility and resiliency
- Diminish the contribution of kidney care to climate change by:
  - Preventing kidney diseases by addressing upstream risk factors, such as access to nutrition, access to care, chronic stress from discrimination and inequality, early detection and intervention of genetic kidney diseases, and co-morbid conditions, such as hypertension and diabetes
  - Researching the environmental footprint of kidney replacement therapies to better understand and mitigate the impact of necessary therapies in clinical practice
  - Utilizing more efficient technologies, including state-of-the-art reverse osmosis modules, which decrease water use, and devices that generate dialysate at the point of care
  - Reducing medical waste, including plastic waste, at every opportunity
  - Increasing the adoption of telehealth and other technologies that lower carbon emissions
  - Fostering the development of new therapies for kidney failure with a focus on environmental sustainability
- Advocate for public policy to address climate change as a contributor to kidney health by:
  - Joining a growing number of medical societies and journals in sounding the alarm and calling on governments to strengthen efforts to meet emissions targets
  - Fostering the development of sustainable dialysis technology and new therapies for kidney failure with a focus on sustainability and allocating funding accordingly
  - Developing guidelines and best practices for incorporating sustainability into clinical practice, including collection and reporting of data on resource use
  - Promoting sustainable procurement practices
  - Reducing barriers to telehealth

The voices of kidney health professionals are critical to bring attention to the growing impact of climate change on kidney health and people with kidney diseases. Kidney health professionals must call for policy and interventions to address climate change. ■

No Filters: Assessing Physician Communication When Discussing Conservative Management of Kidney Failure

By Antonio Gabriel D. Corona and Holly M. Koncicki

Modality selection for treatment of end stage kidney disease (ESKD) is a complex, life-changing decision that patients with chronic kidney disease (CKD) must address. Offering conservative, or non-dialysis therapy, as an option continues to be a challenge for nephrologists. Conversations to discuss this option are held infrequently, due to prognostic uncertainty, a lack of an organizational care framework, and significant emotional attachments (1, 2). In a recent article, Hamroun and colleagues (3) highlight another possible compelling reason: a disproportionate belief in physicians' ability to communicate effectively with patients.

Physicians tend to overestimate their communication proficiency (4). Hamroun and colleagues (3) echo this concern in their article, specifically in the setting of discussing non-dialytic care for patients with advanced CKD. The investigators used data from the CKD-REIN (Renal Epidemiology and Information Network) cohort, which studied 38 nationally representative nephrology clinics in France. Surveys were collected from 137 nephrologists and 1206 patients with CKD stage 4 regarding treatment options for kidney failure. It was found that all participating clinics (100%) reported their ability to offer conservative care for their patients, with more than 70% of these centers routinely providing classes for patients to learn about options for their management. Furthermore, the majority of nephrologists (93%) reported they routinely discuss conservative management with their patients, with 81% of these physicians attesting they were at least fairly comfortable talking about the topic. Despite this, only 5% of surveyed patients reported that their doctor informed them that "no dialysis" was an option. Of the respondents who attended the educational sessions, only 10% claimed they received information about conservative management. There seems to be a marked discrepancy between nephrologists' perceived ability to present information and patients' accounts of the information they received. The consequence of this discrepancy is further accentuated by the low percentage of patients in the cohort (6%) who ultimately opted for conservative care.

Nephrologists may overestimate their success in having goals of care discussions with patients, as patients do not recall these conversations to the same extent, suggesting ineffective communication. A number of studies have glanced at this inconsistency between nephrologists' reported experience and actual practice patterns through the lens of palliative care. Although most nephrologists reported the utmost confidence in their palliative care training, including integrating advance care planning discussions in their routine care of patients with CKD (5), the rate of hospice use for this population lags far behind that of patients with other terminal illnesses, such as cancer, dementia, or lung disease (6).

Hamroun and colleagues (3) cite reasons for this gap in communication, including the inconsistent decision-making styles that nephrologists were found to use to mitigate their own emotional burdens (1, 3) and the vague terminology to describe and advise conservative or palliative care (3). Table 1 outlines strategies to overcome various barriers to effective communication. Moreover, there is hope, according to Hamroun and colleagues (3), that future research can guide nephrologists to implement unfiltered communication strategies to help streamline conservative care information for ESKD patients. ■

Table 1. Strategies to promote effective communication about conservative kidney health care

Barriers to communication in advanced illness	Best-practice recommendations
Timing	Initiate conversations early. Critical events, such as time of diagnosis, treatment complications, or any change in condition, should be opportunities to address advance care planning (7).
Prognostic uncertainty	Identify poor prognostic indicators for CKD and ESKD, including poor functionality and nutritional status. It can be difficult to assess the complex medical conditions of these patients because of multiple factors that portend poorer outcomes; however, anticipation regarding the discussion should not be a reason to avoid it (8). Be prepared to have multiple meetings with patients as the illness trajectory progresses.
Concern for patients losing hope	Recognize that acknowledging patients' poor prognoses is not incongruous with hope. Patients still maintain hope in achieving a good quality of life and fulfilling their end-of-life wishes (9).
Difficulty in broaching the topic	Acknowledge that if there are any feelings of unpreparedness broaching end-of-life conversations, whether due to lack of experience or feelings of attachment, collaborate with palliative care. Palliative nephrology has been shown to meet gaps in care and accomplish patient satisfaction (10).

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Perspective: What Will the Fresenius Merger Mean for Kidney Care?

By Melanie Padgett Powers

Fresenius Medical Care announced in March that it was forming a separate company as part of a three-way merger with InterWell Health and Cricket Health. Through the merger, the largest dialysis provider in the United States will combine with two value-based care companies: a physician organization of more than 1600 nephrologists and a technology start-up. The start-up, Cricket Health, created a patient platform, care-support program, and machine-learning program aimed at identifying kidney disease and predicting disease progression.

"We see value-based care as the future of health care, and this new company will make a dramatic difference for thousands of people," said David Pollack, president, Integrated Care Group, Fresenius Medical Care North America, in a statement to *Kidney News*. "The new InterWell Health expects to improve patients' quality of life through reduced hospital admissions and readmissions, slower disease progression, increased transplant referrals and rates, accelerated transition to home dialysis, and improved health equity. Over the past 5 years, our value-based care programs have reduced hospital admissions by 34%, and planned starts to dialysis in those programs are twice the national average. By leveraging the new InterWell Health's technological innovations and its leading network of nephrologists, we expect to improve on these outcomes in the future."

What will this merger mean for nephrology practices and people with chronic kidney disease (CKD)?

It's been almost 3 years since the federal government launched the Advancing American Kidney Health initiative with the goals of reducing the risk of kidney failure, improving access and quality of person-centered treatment, and increasing transplant access.

As part of these efforts, the Centers for Medicare & Medicaid Services (CMS) launched the voluntary nephrologist-centric Kidney Care Choices model, which includes the Kidney Care First and Comprehensive Kidney Care Contracting options in which dialysis facilities, nephrologists, and other health care providers form accountable care organizations to manage care for beneficiaries with advanced CKD and end stage kidney disease.

With that context and news of the merger, *Kidney News* asked three nephrologists who are tuned into the nephrology marketplace to share their thoughts.

Katie Kwon, MD

Nephrologist in private practice at Lake Michigan Nephrology and vice president of clinical affairs at Panoramic Health (formerly Global Nephrology Solutions). Panoramic Health is a physician-led, value-based kidney care organization with 600 providers in 15 states.

I was not all that surprised to hear about the merger, and I fully expect there to be more mergers in this space. It's been really active in the last 18 months or so and really revving up in the last 6 months as these companies try to get nephrologists on board and participating with the new value-based care payment models.

I thought there were some interesting takeaways from this merger. One of them was how vitally important data analytics and population management are to be successful with these new models. I thought that's what Cricket brought to the merger. It had really invested in not just an electronic medical record (EMR) that does billing—which is what all our EMRs

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Fresenius merger

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have been for so long—but also in taking all the data that have been going into these EMRs and using them to predict who is at risk for bad outcomes and who needs these targeted interventions. That's really, really important to be able to do, and it's extremely expensive.

I think we're seeing with these models that there are enormous market pressures to get one's hands on those analytics, but it's going to have to be large scale. That's why I think there will be more mergers happening, because programming those analytics is so expensive to get right that it's out of reach for medium-sized companies, much less for small practices.

There has been some concern that as dialysis companies establish their own value-based care arms, they may try to "gatekeep" a little bit the patients already undergoing dialysis in their units. So, I think that's an area that hopefully CMS will be watching really closely, because dialysis units are going to be a big part of success in improving their outcomes. And, dialysis is so time consuming that the best place to interact with those patients usually is at their dialysis unit. So, I hope that it will be made crystal clear by the people administering these programs that dialysis patients need to be able to access their value-based care benefits in a company-neutral way and that dialysis companies allow other programs to interact with their programs in their dialysis units. That will be something interesting to watch.

I am hopeful that nephrologists, who were put at the center of these models to drive care, would remain there. I hope as they partner with these different practices that they recognize their expertise has value, their patient panel has value, and they should be partnering with companies that provide them tools but allow them to continue to get their patients what they need. And then, nephrologists should reap the rewards of driving better outcomes for these patients.

Eugene Lin, MD, MS

Assistant professor of medicine at the University of Southern California and a health services researcher with a focus on economic policies pertaining to nephrology.

I think this is an interesting move because it speaks to where Fresenius wants to be competitive. Before this, the market

was mostly start-up companies. It's a high-risk, high-reward sort of game with start-ups, but when you see an established player take a leap, that says a lot about where the market is going. I think Fresenius thinks the future is in care coordination and home dialysis and not just with its status quo business strategy of in-center hemodialysis.

We'll have to see if this changes Fresenius' business model in practice. My hope is that it expands the market with respect to more patient choice.

Medicare and private payers are recognizing that dialysis is expensive, so they're looking for alternatives to what kidney care has traditionally focused on, which is in-center dialysis. We know that, in general, payers have been interested in more coordinated care and accountable care organizations. There has been increasing interest to reduce costs and improve outcomes given how costly this population is and how outcomes are not particularly great.

One can be very cynical about all of this and say Fresenius is just responding to market incentives. But isn't that what people want? Isn't that the point of public policy? Fresenius is recognizing that it's important for the company to adapt. Most people would say that it's a good thing when providers change to improve care.

One of the criticisms of payment models has been that incentives are geared toward dialysis, and there aren't that many incentives for CKD care. I think that's right. The industry is going to build around the market that's created for it. What we have today is a product of two decades-plus of a lot of money going into dialysis care and not a lot of money going into CKD care and transplantation.

The government and payers are realizing that if you want to see the market head to another place, you need to put money there. Providers aren't going to do it out of the goodness of their hearts. Even if providers wanted to do it, if they can't survive financially, it's not going to materialize. So, if we want to see people broadly caring about CKD care, we will likely need broader reforms that move money there.

Suzanne Watnick, MD

Chief medical officer at Northwest Kidney Centers and professor of medicine at the University of Washington in Seattle.

My initial thought was, "Wow, that's going to be a big partnership, and I wonder how it's going to shake up the environ-

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Fresenius merger

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ment." But at the same time, I thought, "Oh, that makes sense, given that we want to move to a more patient-centered care environment."

Overall, my long view is that value-based care is really the way things are going. So, on the one hand I thought this merger is a great way to provide more holistic care to people.

A major concern is how the community moves forward. Hopefully, independent groups will continue to have a voice for the patients they serve.

The pandemic has been so awful for our community. If we look at Medicare data, our patients have had six times more hospitalizations in comparison to other Medicare beneficiaries—and a substantially higher mortality rate.

One of the silver linings of the pandemic for our patients is that the community has really come together in bigger ways than they have before. For example, there's more conversation now among all the chief medical officers around the country. We share ideas, such as how to improve quality, how to improve safety, and how to improve a culture of safety.

It's that context where I think that partnerships are accelerating. There are some big players in the field that are coming together. That has led to some groups scrambling to make deals to make sure that future strategy is going to be implementable with the resources that a group has.

If we look at 2019 to 2021, we definitely saw an increase in home dialysis rates. We don't have finalized numbers yet, but I can relay that in our dialysis organization, we increased over 10% year on year, both in 2020 and 2021, which is amazing even in the setting of staffing shortages and being a small nonprofit with narrow margins.

So, going back to this partnership of Fresenius with InterWell and Cricket, Cricket has always advertised that it can get much higher percentages of patients at home, and Cricket has shown results, even if it's not with large numbers yet. So, it's not surprising that Fresenius would want to partner with Cricket.

If one of Fresenius's goals is to increase numbers of patients going home and then to bring in InterWell so that it has the partnerships to be able to work with patients and their care teams, it makes sense. ■

Open Access Publishing: Who Pays the Price?

By Lauren Floyd, Madelena Stauss, and Alexander Woywodt

Page charges have been in existence across many fields of science for a century or longer, and journals have to cover their costs. Historically, journals have relied on income from subscriptions to cover costs associated with printing, distribution, and other overhead fees, whereas peer review and editorial board activities were free. The funding model for such journals has now undergone unprecedented change. Originally, many journals transitioned gradually into an online-only, paywall-protected existence, as both institutional and individual subscriptions declined. As a result of this development, many researchers and clinicians in low- and middle-income countries lost access to published research or resorted to pay per view. In response, open access (OA) as a concept has, to a large extent, re-established equal access to research, leading to fast and effective dissemination of work globally. However, to compensate for the lack of income through subscriptions and paid views, OA has recently, within a short period of time, created new article-processing fees for authors, which can be as high as $3500 or more (1, 2). In effect, the funding of scientific journals has now changed from a subscription model to one based on fees paid by authors and their institutions (3). We have recently argued that for many authors, these costs are prohibitive, and therefore, the term OA is, to some extent, a misnomer: Authors have lost access to publishing options solely due to lack of funding, leading to unintended bias, unequal access to career opportunities, and distress (1). We suggest that for all of its

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Table 2: Incidence of Overall[a] and Severe[b] Hypoglycemic Events in Placebo-Controlled Clinical Studies[c]

Monotherapy (24 weeks)	**Placebo (n=229)**	**JARDIANCE 10 mg (n=224)**	**JARDIANCE 25 mg (n=223)**
Overall (%)	0.4	0.4	0.4
Severe (%)	0	0	0
In Combination with Metformin (24 weeks)	**Placebo + Metformin (n=206)**	**JARDIANCE 10 mg + Metformin (n=217)**	**JARDIANCE 25 mg + Metformin (n=214)**
Overall (%)	0.5	1.8	1.4
Severe (%)	0	0	0
In Combination with Metformin + Sulfonylurea (24 weeks)	**Placebo (n=225)**	**JARDIANCE 10 mg + Metformin + Sulfonylurea (n=224)**	**JARDIANCE 25 mg + Metformin + Sulfonylurea (n=217)**
Overall (%)	8.4	16.1	11.5
Severe (%)	0	0	0
In Combination with Pioglitazone +/- Metformin (24 weeks)	**Placebo (n=165)**	**JARDIANCE 10 mg + Pioglitazone +/- Metformin (n=165)**	**JARDIANCE 25 mg + Pioglitazone +/- Metformin (n=168)**
Overall (%)	1.8	1.2	2.4
Severe (%)	0	0	0
In Combination with Basal Insulin +/- Metformin (18 weeks[d])	**Placebo (n=170)**	**JARDIANCE 10 mg (n=169)**	**JARDIANCE 25 mg (n=155)**
Overall (%)	20.6	19.5	28.4
Severe (%)	0	0	1.3
In Combination with MDI Insulin +/- Metformin (18 weeks[d])	**Placebo (n=188)**	**JARDIANCE 10 mg (n=186)**	**JARDIANCE 25 mg (n=189)**
Overall (%)	37.2	39.8	41.3
Severe (%)	0.5	0.5	0.5

[a]Overall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL
[b]Severe hypoglycemic events: requiring assistance regardless of blood glucose
[c]Treated set (patients who had received at least one dose of study drug)
[d]Insulin dose could not be adjusted during the initial 18 week treatment period

Genital Mycotic Infections: In the pool of five placebo-controlled clinical trials, the incidence of genital mycotic infections (e.g., vaginal mycotic infection, vaginal infection, genital infection fungal, vulvovaginal candidiasis, and vulvitis) was increased in patients treated with JARDIANCE compared to placebo, occurring in 0.9%, 4.1%, and 3.7% of patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with either JARDIANCE 10 or 25 mg. Genital mycotic infections occurred more frequently in female than male patients (see Table 1). Phimosis occurred more frequently in male patients treated with JARDIANCE 10 mg (less than 0.1%) and JARDIANCE 25 mg (0.1%) than placebo (0%). *Urinary Tract Infections:* In the pool of five placebo-controlled clinical trials, the incidence of urinary tract infections (e.g., urinary tract infection, asymptomatic bacteriuria, and cystitis) was increased in patients treated with JARDIANCE compared to placebo (see Table 1). Patients with a history of chronic or recurrent urinary tract infections were more likely to experience a urinary tract infection. The rate of treatment discontinuation due to urinary tract infections was 0.1%, 0.2%, and 0.1% for placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. Urinary tract infections occurred more frequently in female patients. The incidence of urinary tract infections in female patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg was 16.6%, 18.4%, and 17.0%, respectively. The incidence of urinary tract infections in male patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg was 3.2%, 3.6%, and 4.1%, respectively *[see Use in Specific Populations]*. Clinical Trials in Patients with Heart Failure: The EMPEROR-Reduced study included 3730 patients with heart failure and left ventricular ejection fraction (LVEF) ≤40% followed for a median of 16 months, and EMPEROR-Preserved included 5988 patients with heart failure and LVEF >40% followed for a median of 26 months. In both studies, patients were randomized to JARDIANCE 10 mg or placebo. The safety profile in patients with heart failure was generally consistent with that observed in patients with type 2 diabetes mellitus. *Laboratory Tests:* Increases in Serum Creatinine and Decreases in eGFR: Initiation of JARDIANCE causes an increase in serum creatinine and decrease in eGFR within weeks of starting therapy and then these changes stabilize. In a study of patients with moderate renal impairment, larger mean changes were observed. In a long-term cardiovascular outcomes trial, the increase in serum creatinine and decrease in eGFR generally did not exceed 0.1 mg/dL and -9.0 mL/min/1.73 m^2, respectively, at Week 4, and reversed after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with JARDIANCE. Increase in Low-Density Lipoprotein Cholesterol (LDL-C): Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in patients treated with JARDIANCE. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. The range of mean baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups. Increase in Hematocrit: In a pool of four placebo-controlled studies, median hematocrit decreased by 1.3% in placebo and increased by 2.8% in JARDIANCE 10 mg and 2.8% in JARDIANCE 25 mg treated patients. At the end of treatment, 0.6%, 2.7%, and 3.5% of patients with hematocrits initially within the reference range had values above the upper limit of the reference range with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. **Postmarketing Experience:** Additional adverse reactions have been identified during postapproval use of JARDIANCE. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure: Ketoacidosis; Urosepsis and Pyelonephritis; Necrotizing Fasciitis of the Perineum (Fournier's gangrene); Angioedema; Acute Kidney Injury; Skin Reactions (e.g., rash, urticaria).

DRUG INTERACTIONS:

Table 3: Clinically Relevant Interactions with JARDIANCE

Diuretics	
Clinical Impact	Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.
Intervention	Before initiating JARDIANCE, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating JARDIANCE. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.
Insulin or Insulin Secretagogues	
Clinical Impact	The risk of hypoglycemia is increased when JARDIANCE is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin.
Intervention	Coadministration of JARDIANCE with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.
Positive Urine Glucose Test	
Clinical Impact	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
Intervention	Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay	
Clinical Impact	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.
Intervention	Monitoring glycemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycemic control.

USE IN SPECIFIC POPULATIONS: Pregnancy: *Risk Summary:* Based on animal data showing adverse renal effects, JARDIANCE is not recommended during the second and third trimesters of pregnancy. The limited available data with JARDIANCE in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*. In animal studies, adverse renal changes were observed in rats when empagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 13-times the maximum clinical dose caused renal pelvic and tubule dilatations that were reversible *[see Data]*. The estimated background risk of major birth defects is 6% to 10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20% to 25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Clinical Considerations: *Disease-associated maternal and/or embryo/fetal risk:* Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity. *Data:* Animal Data: Empagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 10, 30 and 100 mg/kg/day caused increased kidney weights and renal tubular and pelvic dilatation at 100 mg/kg/day, which approximates 13-times the maximum clinical dose of 25 mg, based on AUC. These findings were not observed after a 13-week, drug-free recovery period. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development. In embryo-fetal development studies in rats and rabbits, empagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. Doses up to 300 mg/kg/day, which approximates 48-times (rats) and 128-times (rabbits) the maximum clinical dose of 25 mg (based on AUC),

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advantages, OA carries significant risks as well (Figure 1) and propose three strategies to address the issues.

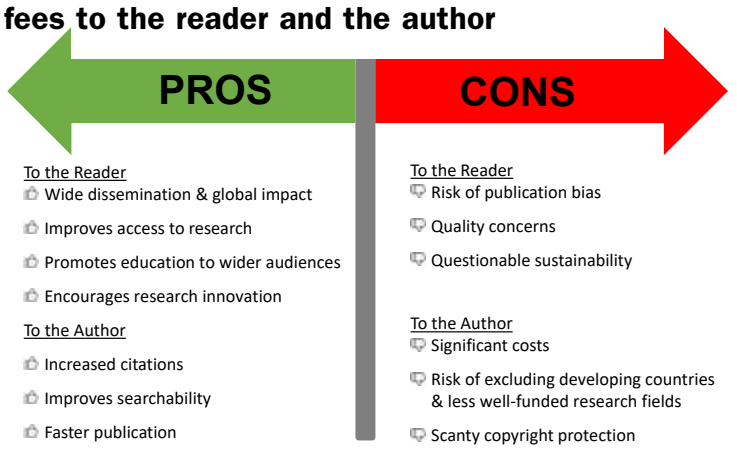
First, journals should be much more transparent about the costs of publishing and the profits that are made. We think authors submitting to the journals but also editors and peer reviewers have a right, to some degree, of insight into funding streams and cost in relation to publication fees.

Second, we would like to encourage journals to rethink their threshold for discounted publication fees, which disadvantages many middle-income countries (4). Additional subsidies and discounts should be considered for students and trainees for work already accepted that cannot be published due to authors' lack of funding.

Third, some journals follow the "platinum open access" model and do not charge fees at all, usually through sponsorship. As a kidney community, we should perhaps consider sending research to these journals as a way of increasing their relevance and supporting their stance on fees. Another interesting approach is self-publication, which is increasingly recognized as a sustainable form of scientific communication (5).

In conclusion, we do not deny the many obvious advantages of OA publishing, but we are concerned about unintended consequences. We fear a situation where research is only published from a smaller pool of institutions, leading to loss of breadth and perspective. We hope that a wider discussion of this topic may help to drive change, leading to an environment where research is published on the basis of scientific merit and not access to funding. ■

Figure 1. Pros and cons associated with open access fees to the reader and the author



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Drs. Floyd and Stauss report no conflicts of interest. Dr. Woywodt is on the editorial board of *Clinical Kidney Journal* and *BMC Nephrology*.

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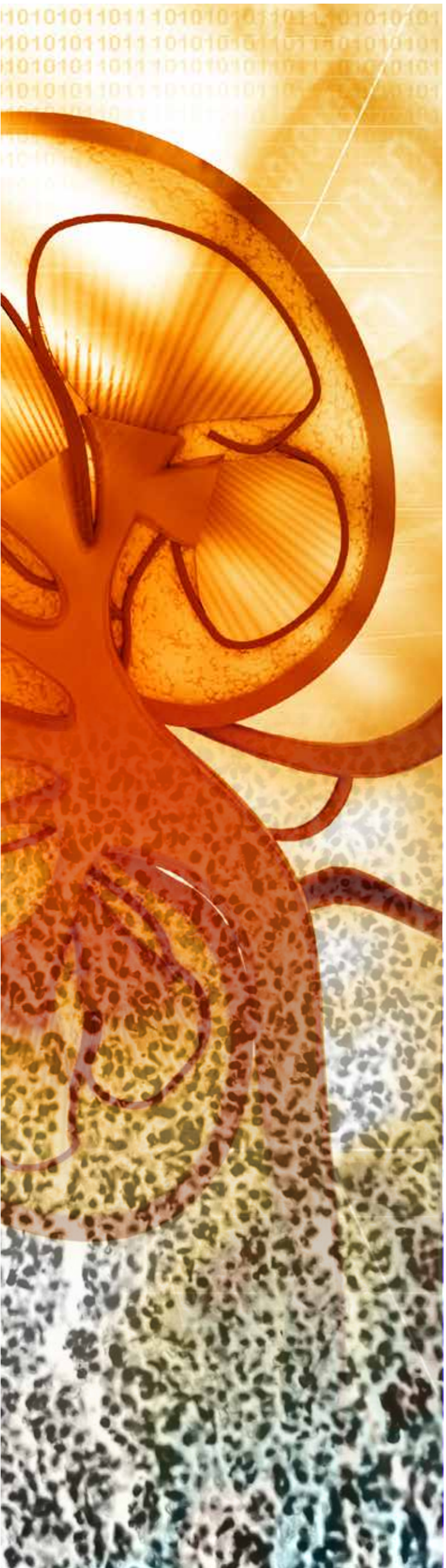

CANCER AND KIDNEY DISEASES

Onconephrology Comes of Age

By Mark A. Perazella and Mitchell H. Rosner

Over the past 10 to 20 years, there has been a revolution in the care of patients with cancer. In addition to classic chemotherapy agents, anti-cancer agents now include targeted therapies and immunotherapies, which harness the power of the immune system. These new therapies have transformed cancer into a chronic disease for many patients. Importantly, acute and chronic kidney diseases, electrolyte and acid-base disorders, and hypertension have become highly prevalent complications in this group of patients. This is particularly true for those with liver cancer, multiple myeloma, renal cell carcinoma, leukemias and lymphomas, and cancer patients treated with potentially nephrotoxic therapies. Many patients who now survive cancer are left with the sequelae of chronic kidney disease. These various intersections of cancer and the kidney have led to the recognition that the fields of nephrology and oncology are intricately linked and that a focus on kidney diseases is needed to improve outcomes and maximize the benefits of these revolutionary therapies. In response to this rapidly growing need, the new subfield of onconephrology was born.

This rapidly growing subspecialty has become an important source of nephrology consultations, as oncology patients now constitute a significant number of patients who nephrologists examine for kidney-related conditions within inpatient hospital floors, medical intensive care units, and outpatient clinics. The growth in the number of patients with onconephrology disorders is a result of two major factors. First, there is an increasing number of patients with cancer, and second, there has been a steady reduction in cancer death rates because of more effective cancer therapies, such as the traditional chemotherapeutic agents, targeted cancer therapies, cancer immunotherapies, and stem cell therapies.

It is notable that onconephrology extends beyond nephrologists and oncologists. Care for oncology patients with kidney diseases has become more specialized and complicated, requiring collaboration among nephrologists, hematologists, oncologists, intensivists, pharmacists, urologists, pathologists, and palliative care specialists. It is illustrative that many of the largest cancer centers in the United States have developed multi-disciplinary clinics that bring together these various specialties to address kidney-related conditions in patients with cancer.

What had been a small group of interested nephrologists (participating in the ASN Onconephrology Forum) has grown into a large number of nephrologists (and other specialists) with expertise in onconephrology. Experts have designed and participated in Onconephrology Symposia at ASN Early Programs and onconephrology conferences at several medical centers specializing in cancer care. Journals focused on onconephrology have emerged (e.g., *Journal of Onco-Nephrology* and *Frontiers in Nephrology: Onconephrology*) and provide a forum for original research, invited reviews, case reports, symposia highlights, debates, and clinical onconephrology images. In fact, most nephrology journals have sections dedicated to onconephrology.

One of the most exciting endeavors in this area is the creation of the American Society of Onconephrology (ASON) by a group of founding members. This new society aims to promote onconephrology research, education, and scholarship for veteran nephrologists, newly minted nephrologists, various trainees (fellows, residents, and students), and other interested health care providers. The goal is to grow a multi-specialty membership, feature monthly educational conferences, hold yearly symposia, and ultimately (and most importantly) improve the care of patients with cancer and kidney diseases. Although such sub-specialization in onconephrology has been a welcome development to improve patient care, it will be incumbent on all nephrology providers to be acquainted with the intersection of the kidney and cancer. ■

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The authors report no conflicts of interest.

Opportunities for Education and Research in Onconephrology in Latin America

By Verônica T. Costa e Silva and Gregorio T. Obrador

Latin America is a vast region of primarily middle- and low-income countries with approximately 660 million people who share a Latin extraction and language (Spanish or Portuguese). The area exhibits extreme diversity in socioeconomic status and access to quality health care. The prevalence of chronic kidney disease (CKD) seems to be growing in Latin America (1). Population aging, suboptimal treatment of comorbidities such as hypertension, and the growing epidemic of type 2 diabetes affect many people in this region. In addition, Latin Americans often live in poverty and follow unhealthy diets, lack physical exercise, and have precarious working conditions (1). Moreover, this population faces difficulties receiving medical care, most often provided by public health systems that struggle with financial constraints.

Cancer incidence is increasing in Latin America, with rising rates of common cancer types, such as breast, prostate, and colorectal cancers (2). Larger countries, such as Brazil, report approximately 620,000 new cancer cases per year. Although significant progress in cancer registries has been made in the last 5 years, quality is heterogeneous because several countries do not have reliable cancer data. Also, the overall population-based cancer coverage in Latin America is 23.3% compared with 98% in North America. Many Latin American patients do not have access to cancer-screening examinations (e.g., mammography, cervical cancer screening, and colonoscopy), leading to delays in cancer diagnosis or access to essential cancer treatments, such as surgery, standard chemotherapy, and palliative care. Furthermore, there is a particular shortage of radiotherapy services. Also, practical strategies to reduce cancer incidence, such as human papillomavirus vaccination, are not broadly available in most Latin American countries (2). Cancer treatment is usually concentrated in tertiary centers located in large metropolitan areas where nephrology training and kidney care of cancer patients typically occur.

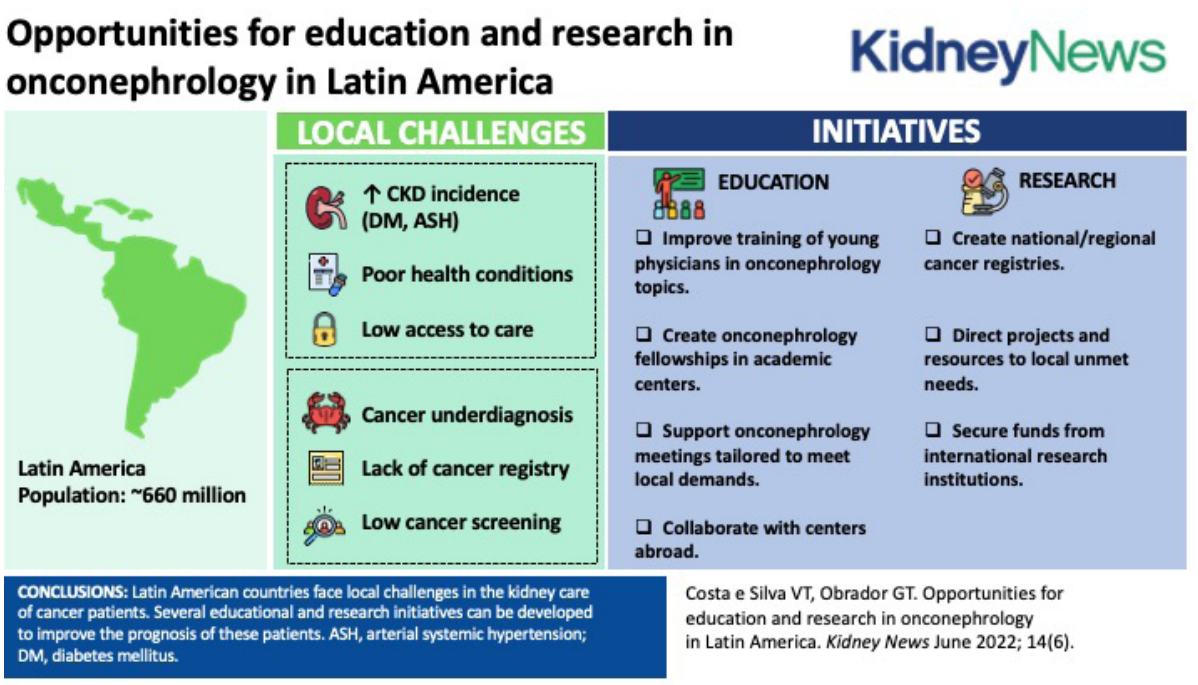
Many Latin American patients do not have access to cancer-screening examinations . . . leading to delays in cancer diagnosis or access to essential cancer treatments.

CKD is common in patients with cancer, and cancer treatment contributes to CKD development and progression. Additionally, CKD has been recognized as a significant risk factor for cancer development and reduced specific cancer survival (3). In Latin American countries, the burden of cancer-associated CKD likely overlaps with local epidemiological determinants (e.g., diabetes, hypertension, and Mesoamerican nephropathy).

Onconephrology is a rapidly expanding field, considered the latest frontier in the fight against kidney diseases. Thanks to a worldwide effort, led mainly through data from North America and Europe, a considerable amount of information has accumulated in the last few years, improving kidney care and hopefully the prognosis of patients with cancer. In Latin America, onconephrology research and education are not yet as well developed, and clinical practice is not as well structured as in high-income countries. Key starting points should include educational and research initiatives (Table 1). With these initiatives in place, we might be able to improve kidney outcomes of patients with cancer in Latin America in the coming years. ■

Table 1. Initiatives for onconephrology education and research in Latin America

Initiatives at the educational level
• Improve the training of internists and general practitioners regarding kidney complications and the care of cancer patients.
• Create onconephrology fellowships and onconephrology groups in academic institutions. Collaborate with centers in the United States and Europe to provide some guidance with this task.
• Support scientific meetings, symposiums, and free online material available to oncology, nephrology, and primary care physicians in the onconephrology field, prioritizing the topics corresponding to local demands.
• Collaborate among centers within Latin America and with centers abroad.
Initiatives at the research level
• Develop local cancer registries (national or regional) and databases detailing kidney outcomes in patients with cancer and implementing strategies that address local needs. A partnership among oncology and nephrology societies can be an effective way to achieve this goal.
• In academic centers, direct projects and resources to local needs, such as the toxicity of cytotoxic drugs (e.g., cisplatin and methotrexate), which is a critical complication of cancer treatment in most Latin American countries.
• Reinforce collaboration with international research institutions that can provide funds to Latin American countries to overcome local budget constraints in developing research projects.



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Onconephrology and Nontraditional Media Education

By Mohamed E. Elrggal and Mohammed Abdel Gawad

The field of onconephrology has recently begun to take shape, and thus, education aimed at onconephrology is still evolving. Importantly, onconephrology was galvanized in the age of social media; thus, non-traditional media is playing a pivotal role in shaping education in onconephrology. For example, the American Society of Onconephrology (ASON) was largely materialized by a group of nephrologists all over the world using WhatsApp to discuss and share cases and forge research collaborations.

The first textbook devoted solely to onconephrology topics was published in 2005 (1) and subsequently, two additional in 2015 (2) and 2019 (3). In addition, the *Journal of Onco-Nephrology* was created in 2017, which represents a reliable source for onconephrology education. However, these forms of traditional media have taken a backseat to free open access medical education (FOAMed) in the last decade.

The first ASN Kidney Week session devoted to onconephrology was held in 2009. This was followed by the first pre-course in 2013 and yearly onconephrology symposia at various US centers thereafter. Kidney Disease Improving Global Outcomes (KDIGO) held its first onconephrology meeting in 2018. Findings presented at these meetings were best disseminated when the meeting policy allowed the audience to "live tweet" and share lectures' contents.

Social media has revolutionized knowledge sharing and education in nephrology, including onconephrology, over the last decade (4). The use of tools, such as Twitter, Facebook, WhatsApp, Slack, and others, has enhanced knowledge exchange, promoted education, and encouraged global collaboration and research (5). Moreover, visual abstracts, videos, podcasts, and spaces have provided more social media engagement than text alone (6). In addition, interactive events, such as online journal clubs, help to disseminate recent advances in medicine (7), and interactive online educational games and online mentorship programs generate interest in the nephrology specialty.

The onconephrology specialty made the best use of FOAMed tools. The interest and education in this field have flourished using social media tools. For example, searching Twitter, using the hashtag #onconeph or #onconephrology, will direct you to hundreds of tweets and tweetorials discussing cases, new articles, webinar slides, and conference materials. Blogs, such as *American Journal of Kidney Diseases* (*AJKD*) Blog, Renal Fellow Network, and NephSIM, contain articles, quizzes, and featured contents specifically for onconephrology. YouTube channels, such as GlomCon and others, contain recorded videos discussing various aspects of onconephrology. Podcasts, such as "Checkpoint NOW," are available for listening and learning anytime. See Table 1 for a complete list of available FOAMed tools and links.

As the field emerges with a limited number of practicing onconephrologists at present, social media tools are needed and are already helping to connect onconephrologists across the globe and to promote education and collaboration. A recent study found that WhatsApp semi-private messaging in a private onconephrology group led to an overall positive learning experience (8).

Hopefully, onconephrology is ripe for more educational innovations in the future. An online onconephrology game, such as NephMadness, can be a great way to increase interest in the subspecialty. An online onconephrology YouTube channel may further increase the learning experience for those interested in the field, and an online certificate in onconephrology is not far from reality. Moreover, education can be expanded to provide additional mentoring to trainees who may aspire to virtual fellowship and training. ■

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The authors report no conflicts of interest.

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Table 1. FOAMed tools in onconephrology

Twitter	#onconephrology and #onconeph **Tweetorials:** **Renal Fellow Network (RFN):** https://www.renalfellow.org/have-a-question-there-might-be-a-tweetorial-for-that/ **Monoclonal gammopathy of renal significance (MGRS):** https://twitter.com/AliMehdiMD/status/1304394512450584576 **Cryoglobulinemia:** https://twitter.com/aishaikh/status/1367541786860740611 **Cyclin-dependent kinase (CDK) 4/6 inhibitors induced acute kidney injury (AKI):** https://twitter.com/ShrutiGkidney/status/1468584593108488194 **Nephrotic syndrome after hematopoietic stem cell transplant (HSCT):** https://twitter.com/AlJurdi/status/1275896844799733761
Blogs	***AJKD*:** https://ajkdblog.org/tag/onconephrology/ **RFN:** https://www.renalfellow.org/
Podcasts	**Checkpoint NOW about onconephrology and immune-mediated nephrotoxicity:** https://podcasts.apple.com/ro/podcast/episode-11-onco-nephrology-and-immune-mediated/id1541046019?i=1000516866525&l=ro
Journals	***Journal of Onco-Nephrology*:** https://journals.sagepub.com/home/jnp
Visual abstracts	Examples: ***Clinical Journal of the American Society of Nephrology*:** https://cjasn.asnjournals.org/content/16/9/1318?with-ds=yes ***Advances in Chronic Kidney Disease*:** https://www.sciencedirect.com/science/article/pii/S1548559521000975
YouTube	**GlomCon:** https://www.youtube.com/c/GlomerularDiseaseStudyTrialConsortium/search?query=onconephrology

Oncohypertension: A New Field in the Making

By Prakash Gudsoorkar

In oncology, survivorship focuses on the health and well-being of a person with cancer from the time of diagnosis until the end of life (1). Hypertension is a growing global public health problem and a contributor to cardiovascular disease (CVD) (2). The relationship among hypertension, cancer, chronic kidney disease (CKD), and CVD is multifaceted, sharing common risk factors, such as smoking, obesity, and metabolic syndrome. For the same reasons, oncohypertension is an emerging subspecialty focusing on the close interplay between hypertension and cancer (3, 4). Hypertension in patients with cancer can be broadly categorized into worsening of preexisting hypertension, paraneoplastic syndrome (i.e., from cancer itself), and hypertension from chemotherapeutic agents and from adjuvant therapies used to treat cancer (Figure 1).

Paraneoplastic hypertension

The prototype example of paraneoplastic hypertension in association with renal cell cancer occurs in 14% to 35% of the cases (5). Pathogenic mechanisms implicated are upregulation of the renin angiotensin aldosterone system (RAAS), ectopic production of erythropoietin, and secretion of vasoactive peptides, such as endothelin 1 and adrenomedullin.

Antihypertensive medications and cancer risk

Over the past few decades, several studies have examined the association between distinct classes of antihypertensive agents and cancer risk. However, each of these observational studies has important caveats and confounders, leaving conflicting results and uncertainty. Even if antihypertensives are associated with a small increased risk of cancer (e.g., thiazides and calcium channel blockers: skin cancer; angiotensin receptor blockers: lung cancer), they likely do not outweigh the known cardiovascular and mortality benefits (6).

Hypertension from cancer therapy

To prevent acute and long-term cardiovascular effects, optimal and timely management of hypertension in survivors of cancer cannot be overstated. Antihypertensive therapies need to be tailored to underlying comorbidities, such as diabetes, heart failure, and others. Hypertension is one of the most common vascular toxicities (class effect) seen in 25%–30% of patients treated with vascular endothelial growth factor inhibition (VEGFi; e.g., bevacizumab, sorafenib, and sunitinib) (7). It is mediated by vasoconstriction (decreased production of endothelial nitric oxide synthase [eNOS]), decreased vascular compliance, and kidney injury (e.g., thrombotic microangiopathy phenotype) (Figure 2).

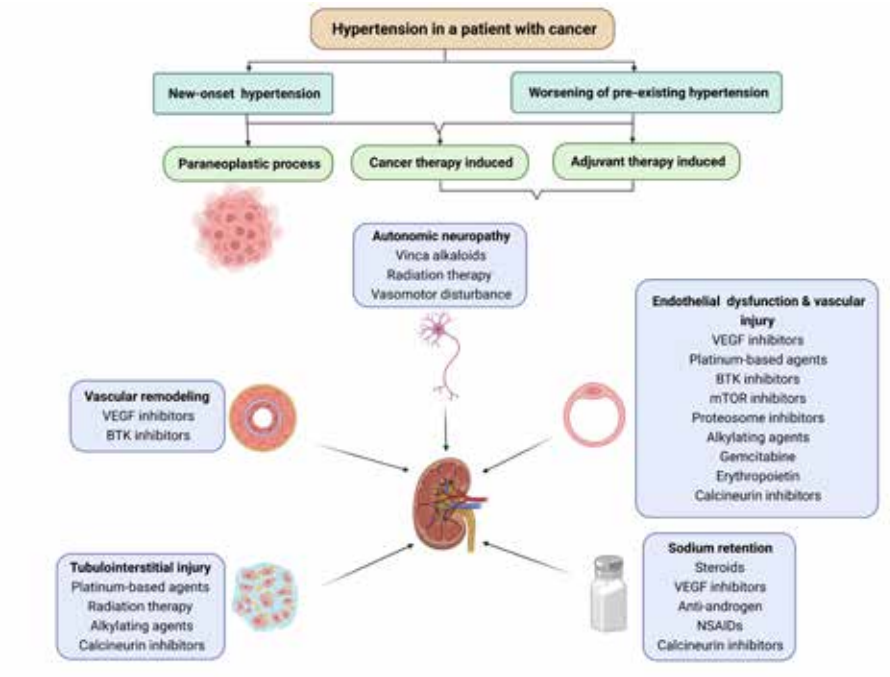
Polymorphisms in the VEGF gene predispose certain patients to the vasculotoxic effect of VEGFi, for example, single nucleotide polymorphisms in Egl nine homolog 3, epidermal growth factor, WNK lysine-deficient protein kinase 1, and the kinase insert domain receptor gene (8). The current data obtained from clinical trials and physiological studies suggest that dihydropyridine calcium channel blockers (avoid diltiazem or verapamil and inhibit cytochrome P450 3A4 leading to higher levels of drugs, such as sunitinib and sorafenib) and RAAS blockers can be considered as first-line antihypertensive therapies for hypertension mediated by VEGFi (Figure 3) (9). RAAS blockers directly cause vascular smooth muscle relaxation and upregulate NO production leading to microcirculatory changes and decreased blood pressure. In addition, angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) help reduce proteinuria that commonly occurs with VEGFi.

Radiation exposure and hypertension

Radiation therapy that involves the head or neck can lead to baroreflex failure and to associated difficult-to-treat labile hypertension and hypertensive crisis (10). Radiation nephropathy occurs in approximately 20% of irradiated subjects and can have various clinical presentations, such as acute radiation nephritis, chronic radiation nephropathy (chronic thrombotic microangiopathy), malignant hypertension, and benign hypertension.

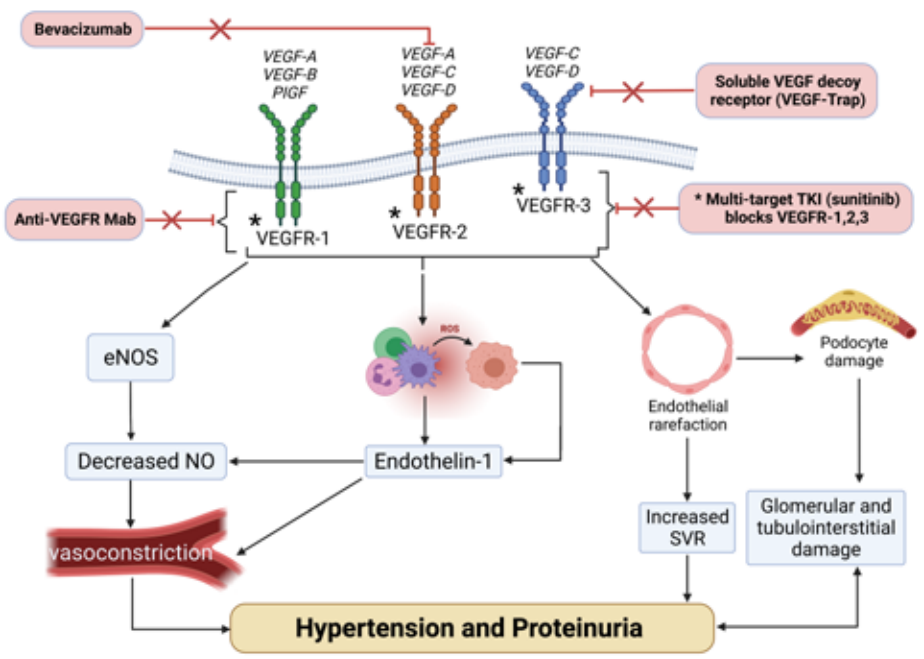
Oncohypertension is an emerging subspecialty in the field of onconephrology and cardio-oncology, as hypertension lies at the intersection of both specialties. Hence, a multidisciplinary team—consisting of oncologist, nephrologist, cardiologist, pharmacist, and primary care physician—should form the framework of an oncohypertension clinic. ■

Figure 1. Hypertension in a patient with cancer



BTK, Bruton tyrosine kinase; mTOR, mechanistic target of rapamycin; NSAIDs, non-steroidal anti-inflammatory drugs. Figure created using Biorender.com.

Figure 2. Pathophysiology of development of hypertension and proteinuria from VEGFi



Mab, monoclonal antibody; PIGF, placental growth factor; ROS, reactive oxygen species; SVR, systemic vascular resistance; TKI, tyrosine kinase inhibitor; VEGFR, VEGF receptor. Figure created using Biorender.com.

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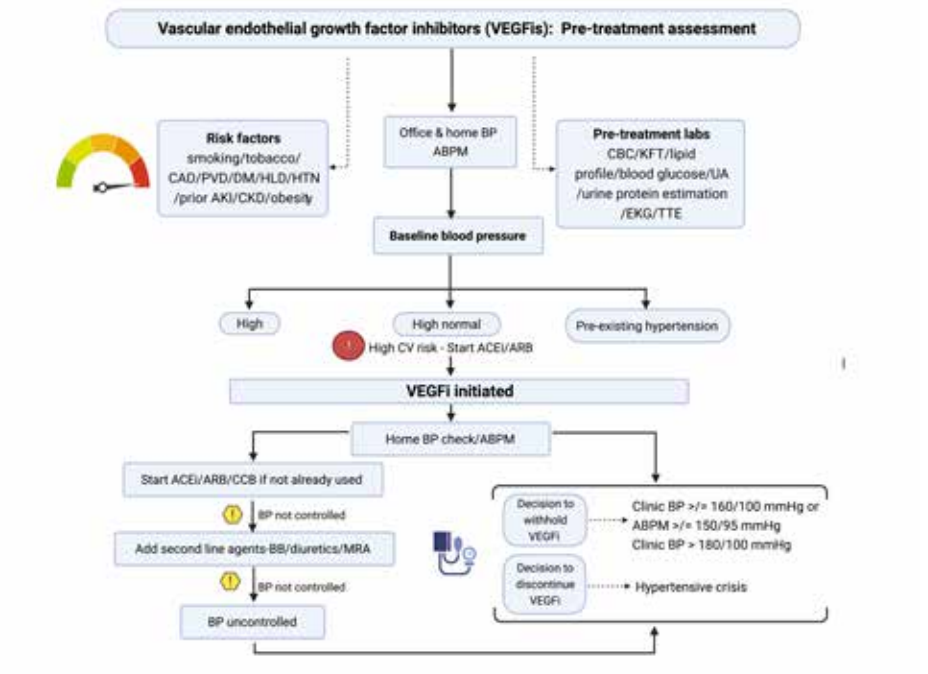
Figure 3. Approach to management of hypertension from VEGFi



ABPM, ambulatory blood pressure monitoring; AKI, acute kidney injury; BB, beta blocker; BP, blood pressure; CAD, coronary artery disease; CBC, complete blood count; CCB, calcium channel blocker; CV, cardiovascular; DM, diabetes mellitus; EKG, electrocardiogram; HLD, hyperlipidemia; HTN, hypertension; KFT, kidney function test; MRA, mineralocorticoid receptor antagonist; PVD, peripheral vascular disease; TTE, transthoracic echocardiography; UA, urine analysis. Figure created using Biorender.com.

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Perspective on Onconephrology from a Cancer Doctor

By Oscar B. Lahoud

In the past decades, the field of hematology-oncology has greatly evolved, bringing to practice the routine use of novel therapies with various mechanisms of action, including chemotherapeutic, immunotherapeutic, and targeted agents, which are often combined into complex regimens (Figure 1).

With these ongoing advances, unique drug-drug interactions, treatment timing, dosing challenges, as well as toxicity profiles have emerged, requiring more advanced expertise from our subspecialty consultants who co-manage these patients. My practice focuses on patients with hematologic malignancies, with a particular interest in plasma cell dyscrasias. These encompass a large spectrum of diseases with unique presentations, a wide range of potential organ involvement, as well as multiple distinct treatment options that combine traditional chemotherapeutic agents with the most novel cellular therapies. Impaired kidney function in a patient with plasma cell dyscrasia could be attributable to any of the following:

- worsening of the disease, leading to monoclonal immunoglobulin deposition in the renal tubules
- amyloid fibrils depositing in the glomeruli, causing nephrotic syndrome
- thrombotic microangiopathy from a calcineurin inhibitor after an allogeneic hematopoietic stem cell transplant
- syndrome of inappropriate anti-diuresis related to the use of an alkylator (cyclophosphamide or melphalan)
- acute interstitial nephritis caused by treatment (e.g., lenalidomide) or other supportive drugs (e.g., anti-microbials and contraindicated non-steroidal anti-inflammatory drug analgesics)
- autoimmune nephritis for a patient in an immunotherapy trial
- complex nephrotoxicity from other chemotherapy (e.g., cisplatin)

The intricacies in determining the cause of kidney dysfunction and optimal course of management demand true experts in the field.

To better serve our most challenging patients, at our institution, we have established monthly, multi-disciplinary amyloidosis tumor boards that include subspecialized hematologists, pathologists, oncocardiologists, and onconephrologists who partake as an integral part of our collective discussion and treatment of patients. On a personal basis, having reliable, devoted onconephrologists working with our group affords us the essential reassurance so that we can focus medical decision-making on the very best personalized therapeutic intervention for our patients, knowing our colleagues will be there to prevent and/or address any potential kidney complication that might arise. Oncologists and general nephrologists alike have come to depend on the expertise of onconephrologists for the elaborate evaluation and management of cancer patients with kidney diseases. Onconephrologists have naturally become an indispensable part of cancer care. As the scope of practice for medical academicians has narrowed down to one's exclusive area of research and clinical proficiency, academic onconephrologists have emerged to lead and work together with other oncologic subspecialists to collaboratively advance the field and enhance the care of the patients we serve. ■

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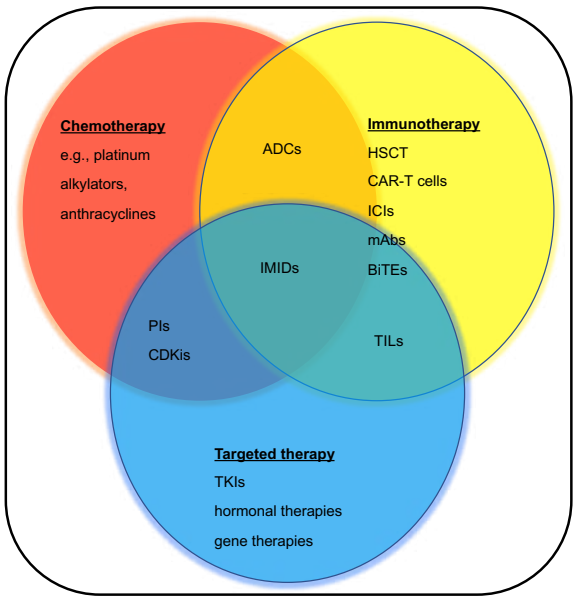
Figure 1. Examples of cancer-directed therapies



Therapies include chemotherapy, immunotherapy, and targeted therapies, as well as examples of hybrid agents. ADCs, antibody-drug conjugates; BiTEs, bispecific T-cell engagers; CAR-T cells, chimeric antigen receptor T-cells; CDKis, cyclin-dependent kinase inhibitors; HSCT, hematopoietic stem-cell transplantation; ICIs, immune checkpoint inhibitors; IMIDs, immunomodulating drugs; mAbs, monoclonal antibodies; PIs, proteasome inhibitors; TILs, tumor-infiltrating lymphocytes; TKIs, tyrosine kinase inhibitors.

Should a Kidney Transplant Be Performed in a Patient with Multiple Myeloma?

By Jaya Kala

Kidney injury and kidney failure are frequently found in patients with multiple myeloma. With the introduction of novel agents in the last two decades, the outcome of patients with multiple myeloma has tremendously improved. The median survival has reached 7.7 years for patients under the age of 65 years (1). Despite the advances in therapies, patients continue to develop end stage kidney disease (ESKD). The survival of myeloma patients on dialysis is inferior to those without myeloma. Because of poor prognosis of multiple myeloma, kidney transplantation has not been considered an option (2). However, with evolving therapies for multiple myeloma, which have significantly improved the progression-free survival and overall survival of patients, it would be reasonable to consider patients with multiple myeloma with advanced chronic kidney disease for eligibility of kidney transplant (3). With improved understanding of risk stratification, clinical prognostic factors, and prediction of early relapse based on genetic testing, an informed decision regarding candidacy of patients with multiple myeloma for kidney transplantation is feasible (4).

Over the last 18 years, several cases have been reported describing patients with multiple myeloma undergoing kidney transplantation after chemotherapy and/or stem cell transplantation (SCT). Patients' characteristics and outcomes that were reviewed are shown in Table 1. Due to missing data, percentages did not always add up to 100%. Of the 58 cases reviewed, over a 1- to 5-year follow-up, 43 patients underwent chemotherapy with SCT, and 13 experienced chemotherapy alone. After kidney transplant with 28 living donors and 23 deceased donors, relapse of multiple myeloma was seen in 50% (29 of 58) and graft loss in approximately 25% (15 of 58), and approximately 32% (19 of 58) died. The wait period for kidney transplant varied from 4 months before to 13 years after remission. As a result of the rapidly changing treatment landscape, the regimens used varied significantly among the patients. The cytogenetic risk and minimal residual disease status were unknown in these patients.

Because of the low number of patients analyzed and significant heterogenicity between studies, no clear conclusion about factors impacting recurrence, death, or graft loss can be made. With improved survival with multiple myeloma, there is a need to address the burden of ESKD, and transplant is a logical strategy. However, heavy immunosuppression for SCT before kidney transplant can increase incidence of myeloid and non-myeloid neoplasms (5, 6). Newly introduced immunomodulators for multiple myeloma can lead to organ rejection. Therefore, while considering kidney transplantation in multiple myeloma patients, several pros and cons need to be examined (Table 2). Although robust data for this unique group of patients are not available, a risk-adapted approach could be used, as proposed, based on expert opinion (Figure 1). A careful evaluation for kidney transplant after multiple myeloma remission is appropriate (6).

The diagnosis of multiple myeloma should not be considered as an absolute contraindication for kidney transplant. A multidisciplinary approach with the transplant team and hematology both before and after transplant are crucial to maximize the chances of success for these individuals and maximize years gained from transplanted organs. With an ever-expanding wait list, organ shortage, and prolonged wait times, careful consideration of transplant candidates must be made. ■

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Dr. Kala serves on a speaker panel for BTG International.

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Table 1. Published reports of outcomes of multiple myeloma patients after kidney transplantation

Reference	Patients, No.	Follow-up, month	Myeloma Rx pre-KTx	Hematological response pre-KTx	Maintenance treatment for MM	Remission to KTx, month	KTx induction	KTx donor type	Relapse of MM, No.	Death, No.	Graft loss, No.
Le et al. (7)	4	16–58	4 Chemo + SCT	1 VGPR, 3 CR	2 Bortezomib 2 None	20–66	No data	No data	1	0	0
Lum et al. (8)	2	13–25	2 Chemo	1 CR, 1 active	2 Bortezomib	12, 0	Basiliximab	2 Living	0	0	0
Shah et al. (9)	5	48–56	5 Chemo + SCT	3 VGPR, 2 CR	No data	14–166	No data	3 Living 2 DBD	3	2	3
Huskey et al. (10)	4	10–72	1 Chemo, 3 Chemo + SCT	3 VGPR, 2 CR	2 Lenalidomide 1 Bortezomib	–4 to –36	2 Basiliximab 2 Alemtuzumab	2 Living 2 DBD	4	1	2
Hedvat et al. (11)	3	36–47	3 Chemo + SCT	No data	No data	20–46	No data	No data	1	1	1
Kormann et al. (2)	13	51.7	8 Chemo + SCT, 3 Chemo	13 VGPR/CR	No data	39–159	3 ATG 10 Basiliximab	2 Living 11 DBD	7	5	6
Heybeli et al. (1)	12	40	6 Chemo + SCT, 6 Chemo	8 CR. 2 VGPR, 2 PR	3 Lenalidomide	6–60	4 ATG 8 Basiliximab	2 Living 11 DBD	9	5	3
Dinh et al. (6)	10	44	10 Chemo + SCT	1 VGPR, 9 CR	3 Bortezomib 1 Lenalidomide 2 Daratumumab 1 Carfilzomib 0 None	7–66	4 ATG 6 Basiliximab	8 Living 2 DBD	3	3	0
Leung et al. (12)	1	92	Chemo	No data	No data	No data	No data	Living	1	1	0
Sánchez Quintana et al. (13)	2	48	2 Chemo + SCT	1 CR 1 VGPR	2 Lenalidomide	48	No data	2 DBD	0	0	0
Domínguez-Pimentel et al. (14)	1	98	Chemo + SCT	No data	Lenalidomide	30	Basiliximab	DBD	0	1	0
Beitinjaneh et al. (15)	1	60	Chemo + SCT	CR	None	36	No data	Living	0	0	0
Total	**58**	**10–98**	**43 Chemo + SCT, 13 Chemo**	**27 CR, 21 VGPR, 3 PR, 2 Active**	**8 Bortezomib 9 Lenalidomide 2 Daratumumab 1 Carfilzomib**	**–4 (KTx before CR) to 166**	**28 Basiliximab 2 Alemtuzumab 11 ATG**	**28 Living 23 DBD**	**29**	**19**	**15**

ATG, anti-thymocyte globulin; Chemo, chemotherapy; CR, complete remission; DBD, donation after brain death; KTx, kidney transplantation; MM, multiple myeloma; PR, partial response; Rx, prescription; SCT, stem cell transplantation; VGPR, very good partial response. Column totals may not add up owing to missing data.

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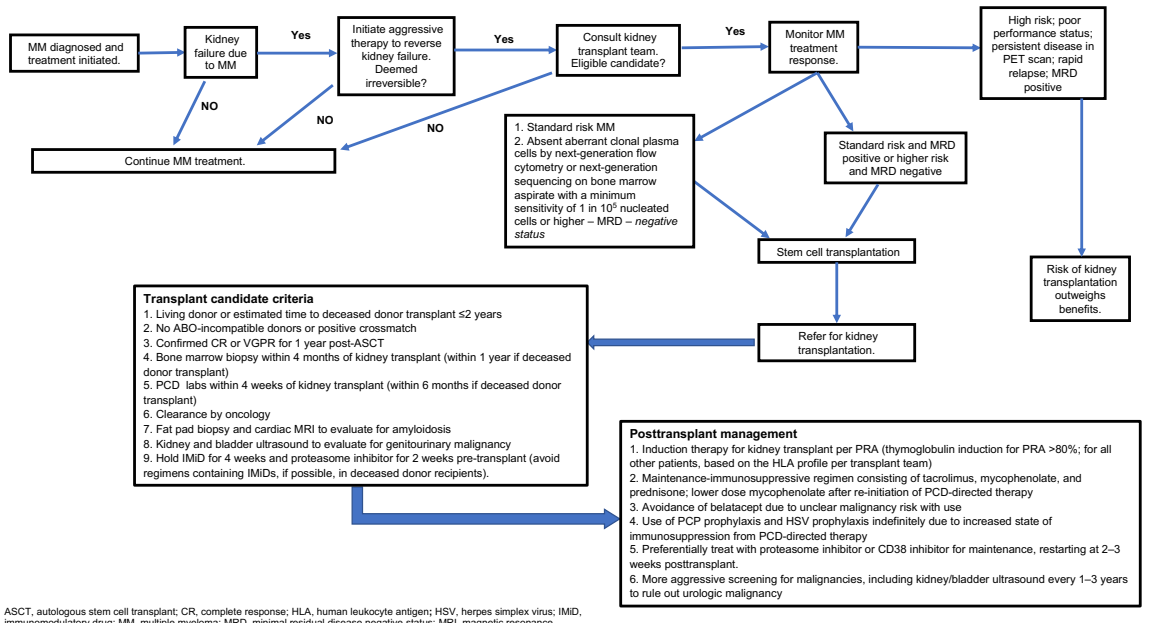
Table 2. Favorable and unfavorable factors for kidney transplant in the multiple myeloma patient

Favorable factors	Unfavorable factors
Improved risk stratification of multiple myeloma now available	Expanding wait list and organ shortage; prolonged wait times
Predicting relapse of multiple myeloma possible based on genetic testing	Some studies show survival of ESKD with multiple myeloma is only 18 months.
Improved relative survival after multiple myeloma treatment	Poor prognostic factors and specific chromosomal abnormalities may be needed to indicate low- versus high-risk myeloma.
Better outcomes after SCT in those with kidney disease	SCT increased risk of secondary malignancy by 4- to 11-fold at median follow-up of 40 months.
Cancer standardized mortality is higher for multiple myeloma patients on dialysis.	Treatment options after transplantation may be limited.
Improved survival with multiple myeloma treatment but suboptimal outcome on dialysis	Immunomodulatory agents for multiple myeloma may lead to organ rejection.
Favorable cost/benefit of kidney transplant versus dialysis	Need to weigh risk versus benefit, because only case series or reports published; no large studies.
Careful consideration of kidney transplantation is appropriate after review by multidisciplinary team.	Consider in select patients with minimal co-morbidities, low risk, s/p SCT with CR for 1–2 years; rare patient

CR, complete remission; s/p, status post (4, 5).

Figure 1. Proposed evaluation of multiple myeloma patient and kidney failure and follow-up



ASCT, autologous stem cell transplant; CR, complete response; HLA, human leukocyte antigen; HSV, herpes simplex virus; IMiD, immunomodulatory drug; MM, multiple myeloma; MRD, minimal residual disease negative status; MRI, magnetic resonance imaging; PCD, plasma cell dyscrasia; PET, positron emission tomography; PRA, panel-reactive antibody; VGPR, very good partial response (6, 10).

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A Path to Training in Onconephrology

By Omar Mamlouk, Marco Bonilla, and Shveta Motwani

Over the past few decades, there has been rapid advancement in the care of cancer patients with a steady flow of novel therapeutics introduced into clinical practice. Accompanying the new therapies are myriad unintended treatment-related effects, some of which have involved the kidneys, electrolytes, acid-base balance, and blood pressure control. There has also been a shift in the mindset of the treating physicians (oncologists and nephrologists) to attempt a pathophysiological understanding and nuanced management of such treatment-related effects rather than binary labeling of drugs into "nephrotoxic" and "non-nephrotoxic" and discontinuation of therapy thought to be nephrotoxic. This evolution in thinking has led to the formation of multidisciplinary teams with nephrologists—onconephrologists—viewed as integral members of the team. Thus, the field implores nephrologists to dig deep and apply principles of renal physiology and pathology to this medically complex patient population.

Becoming an onconephrologist entails either pursuing an onconephrology track within the 2-year nephrology fellowship or completing an additional year of onconephrology clinical or research fellowship.

A career in onconephrology allows ample advantages. Primary drivers for most nephrologists entering this subspeciality are the high complexity and acuity, the cross-disciplinary collaboration in caring for a vulnerable patient population, and the fertile ground for research. Critical to training in onconephrology is the steady-flow referrals of patients with cancer being treated with a wide range of therapies so that the trainee can gain experience in identifying and managing kidney complications of such treatment. In addition, the necessary learning includes collaborating with oncologists to develop a pathophysiological rationale and approaches to treatment that may have limited backing in the form of traditional published evidence (e.g., monoclonal gammopathy of renal significance often requires significant advocacy on the part of the nephrologist for treatment with chemotherapy that is generally administered by oncologists). To streamline such learning, nephrology trainees or nephrologists who desire to gain expertise in this field need to train with qualified experts. Thus, training in onconephrology is often more efficient at, but not limited to, large academic programs with attached cancer centers. Not all nephrology training programs have experts in onconephrology who can mentor trainees. However, this presents job opportunities for graduating onconephrologists to start their careers as the inaugural onconephrologists at such centers.

Becoming an onconephrologist entails either pursuing an onconephrology track within the 2-year nephrology fellowship or completing an additional year of onconephrology clinical or research fellowship (Table 1). The onconephrology track allows the nephrologist to home in on a niche and practice as an expert soon after graduation. Although completion as part of the 2-year fellowship is reasonable, pursuing an additional, dedicated 1-year fellowship offers the trainee time and patient volume to develop experience and gain in-depth learning in the specialty. It also allows for protected time and/or resources to participate in scholarly activities. Some programs may also include formal clinical research training as part of the curriculum. In addition to core training, elective rotations during the fellowship allow fellows to acquire specific exposure to patients with common subtypes of kidney-related complications who are referred to an onconephrology clinic. These rotations can be tailored based on fellow interest and include rotations, for example, through inpatient and outpatient stem-cell transplant to learn about transplant-related adverse effects on the kidney, through melanoma to learn about immunotherapy nephrotoxicity, and through multiple myeloma to learn about myeloma and paraproteinemia-related renal manifestations. Furthermore, completion of a fellowship in onconephrology will help build the fellow's resume and help him or her become a more attractive candidate for job applications, especially in academia. It is important to note, however, that such a dedicated year of training is not a requirement to become an onconephrologist.Although there are clear advantages, there are also some disadvantages of the additional year of onconephrology to consider. First, there are only four onconephrology fellowship programs in North America. Thus, the trainee may need to relocate from his or her fellowship program. Second, as with other fellowships, the financial aspect needs to be considered (i.e., another year of fellow's salary!). Third, the onconephrology fellowship is not accredited by the Accreditation Council for Graduate Medical Education. Fourth, compared with spending additional years in research fellowship, the 3 to 6 months of research time during the year of onconephrology fellowship allow for little opportunity to perform highly impactful work. The research projects in such a short time are generally limited to observational studies (mostly retrospective) or review articles. Last, even with the additional time spent gaining expertise and the need for lifelong learning to manage this medically complex population, the reimbursement for onconephrology patients is identical to that of general nephrology patients. With the exception of a couple of programs in the United States, the vast majority of jobs also require a variable amount of general nephrology care experience (clinic, inpatient service, and dialysis rounding) to generate a salary commensurate with non-onconephrology-specialized peers. Thus, the value of becoming a regional or an institutional expert and referral point person in onconephrology is largely non-financial.

Regardless of the path a trainee takes into onconephrology, it must be accomplished alongside experts in the field. This is especially important given the scarcity of established guidelines on the management of cancer-related kidney diseases that make up onconephrology, thereby stressing the importance of expert opinion. We hope that more trainees will gain interest in this rapidly growing and incredibly gratifying subspecialty within nephrology. ■

Table 1. Advantages and disadvantages of two onconephrology training tracks

Onconephrology training	Pros	Cons
As a track/focus within a 2-year nephrology training program	• Fewer overall years training • Financially advantageous to graduate fellowship • Earlier clinical career in the field upon graduation	• Limited involvement in prospective clinical trials • Limited research opportunities
As a 1-year onconephrology fellowship after 2-year nephrology training	• More relevant clinical experience • Adequate time to participate in scholar activities and receive clinical research training • Competitive resume	• Relocation given the limited number of fellowship programs • Non-accredited fellowship • Limited research time compared with research fellowship track

Omar Mamlouk, MBBS, completed his nephrology fellowship at The University of Texas McGovern Medical School. During the fellowship, he had the opportunity to rotate at MD Anderson Cancer Center and developed an interest in onconephrology. He decided to pursue a 1-year onconephrology fellowship at MD Anderson Cancer Center to expand his knowledge of kidney diseases associated with cancer and cancer therapies, with special interest in immunotherapy-associated kidney toxicity. After graduation, he joined the Section of Nephrology at The University of Texas MD Anderson Center in Houston as faculty.

Marco Bonilla, MD, currently is a second-year nephrology fellow at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY, with an onconephrology and glomerular disease track. Since the beginning of his fellowship and under his mentor's guidance, he has been part of a dedicated onconephrology clinic and developed many collaborative partnerships with experts at a national and international level, thus creating a niche and tailoring his future academic career in this field. He will be joining an academic center in July 2022 with a vision to embark on onconephrology at that center.

Shveta Motwani, MD, MMSc, completed her nephrology fellowship at the Brigham and Women's and Massachusetts General Hospitals combined program in nephrology. Her interest in onconephrology began in her second year of internal medicine residency, and she organized her fellowship rank order list keeping this intention front and center. Starting in her second year of fellowship, she entered the continuity clinic in onconephrology and began formal training in research with the master's program in clinical and translational investigation at Harvard Medical School. After graduating from fellowship, she practiced as an onconephrologist at the Dana-Farber Cancer Institute and Brigham and Women's Hospital for 6 years, which concluded in March 2022. As of April 2022, she became the Director of Onconephrology at Lahey Hospital & Medical Center, Burlington, MA, to create an onconephrology program at that hospital.

The authors report no conflicts of interest.

When Does MGUS Become MGRS?

By Jyotsana Thakkar

Monoclonal gammopathy of unknown significance (MGUS), commonly considered a benign condition, is characterized by a low level of detectable monoclonal immunoglobulin (Ig) in the serum (<30 g/L) and <10% monoclonal plasma cells on bone marrow biopsy. Assuming these low levels of circulating Igs do not cause any end organ damage, treatment is usually not recommended for MGUS. However, in some patients with MGUS, these low levels of Ig or kappa/lambda light chains can cause direct kidney deposition or activation of complements leading to kidney diseases. Because of this, in 2012, the term "monoclonal gammopathy of renal significance" (MGRS) was coined to recognize the spectrum of kidney diseases from MGUS and to treat accordingly (1).

In a recently published retrospective study in the *Clinical Journal of the American Society of Nephrology*, Yong and colleagues (2) describe the histopathological and clinical features of this entity. In this single-center study (performed in China), approximately 700 patients with monoclonal gammopathy who underwent single kidney biopsy were retrospectively examined over a period of 21 years (1999–2020). Thirty-eight percent of patients were classified as having a MGRS-related lesion, whereas the rest (62%) did not have MGRS.

Ig monoclonal protein-related amyloidosis was the predominant kidney lesion seen in most patients (63%), followed by monoclonal immune deposition disease (9%) and thrombotic microangiopathy (8%). In the non-MGRS group, membranous nephropathy (40%) was the most common, followed by IgA nephropathy (14%) and diabetic nephropathy (9%).

In the MGRS group, a higher percentage of patients had proteinuria >1.5 g/d (81% vs. 70%) and a higher prevalence of hypoalbuminemia <3 g/dL (61% vs. 52%) compared with the patients with a non-MGRS lesion. The prevalence of hypertension, diabetes, and hematuria was less in the MGRS group. A free light-chain ratio (normal range 0.2–2.9) was significantly abnormal (odds ratio, 5.57; 95% confidence interval, 2.90–10.69; P = 0.001) in the MGRS subgroup, which had been verified by a previous study done at the Mayo Clinic (3). The authors also compared clinical data for patients with Ig amyloidosis and non-amyloidosis MGRS. Patients with amyloidosis were significantly older and more likely to have hypoalbuminemia and nephrotic-range proteinuria than the non-amyloidosis group.

The authors concluded that the presence of abnormal free light chains, advanced age, and proteinuria >1.5 g/dL is the potential clinical indicator and can point toward the diagnosis of MGRS.

Yong et al. (2) reported similar findings as the Mayo Clinic, except that the hematuria was also significantly associated with MGRS in the Mayo Clinic study (3). This is contrary to the study by Yong et al. (2), where incidence of hematuria was less in the MGRS group than in the non-MGRS group. One possible explanation for such a difference could be a higher incidence of glomerulonephritis and IgA nephropathy in the Chinese population, leading to more hematuria in the non-MGRS group.

The Yong et al. (2) study found a high incidence of an MGRS-related lesion (approximately 40% vs. 60% non-MGRS) in patients with monoclonal gammopathy and kidney diseases, thus necessitating the need for kidney biopsy to diagnose otherwise missed cases of MGRS. We cannot rule out the possibility of diagnostic bias, since all patients with MGRS underwent kidney biopsies in the study. The salient clinical characteristics differentiating MGRS from non-MGRS kidney biopsy lesions include older age, greater proteinuria (>1.5 g/d), and an abnormal free light-chain ratio among the MGRS group. Nephrologists should be aware of these clinical associations to help in the diagnosis and management of MGRS with kidney disease.

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The author reports no conflicts of interest.

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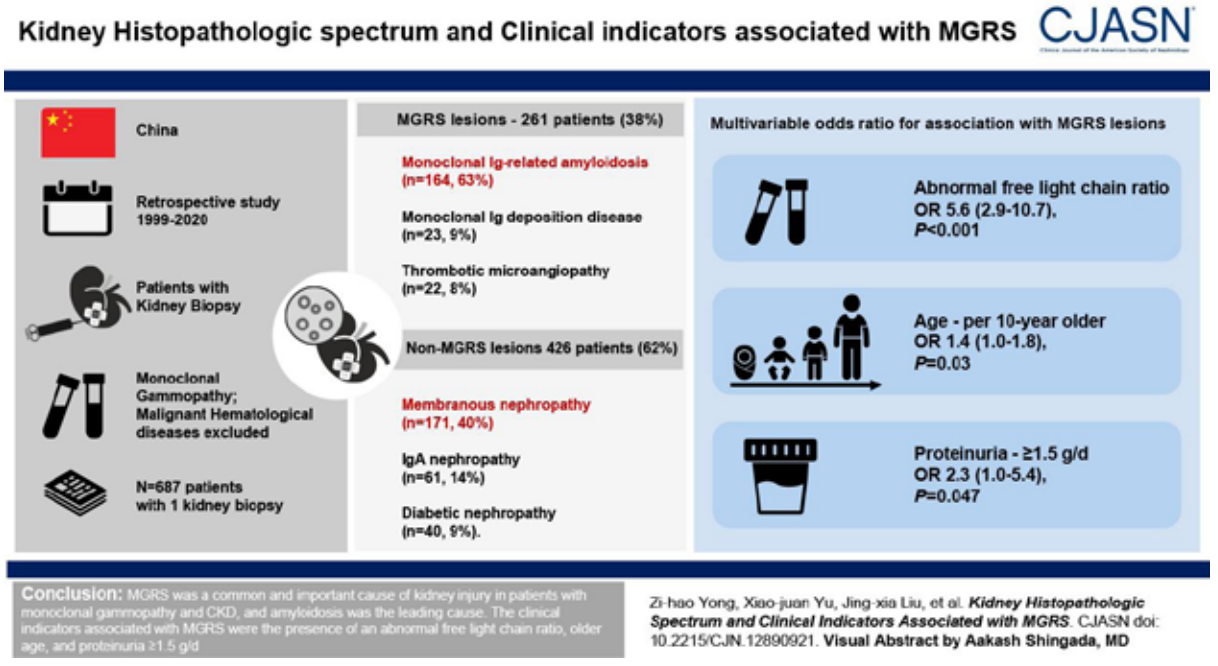

Reconsidering All Aspects of Nephrology's Future

By Melissa West

Earlier this year, ASN received requests from the American Board of Internal Medicine (ABIM) and Accreditation Council for Graduate Medical Education (ACGME) that taken separately would impact the future training of nephrologists. After careful consideration and thought, the ASN Council responded with a request for 8 months to convene the community and reconsider all aspects of the future of the specialty of nephrology.

"This is a unique opportunity to respond to the requests of ABIM and ACGME. Nephrology has evolved over the last 5 to 10 years as more options to treat patients earlier have become available," said former ASN President Mark E. Rosenberg, MD, FASN. "Advancing American Kidney Health focused the community on patient choice, including options for home dialysis, reforming transplant policy, accelerating innovation, and eliminating disparities."

Dr. Rosenberg is chairing the ASN Task Force on the Future of Nephrology, which is charged with meeting the society's commitment to ABIM and ACGME. The task force includes a diverse cross-section of ASN members, such as current and former nephrology fellowship training program directors, nephrologists in private practice, leaders in academic medicine, and early career nephrologists. According to Dr. Rosenberg, the task force will interact with representatives from ABIM and ACGME as appropriate."

The ASN Task Force on the Future of Nephrology is not intended to serve as a representative panel of every constituency within nephrology. Rather, ASN will facilitate deep dives and opportunities for community members to provide their input. Some of the groups that the task force will be interacting with include the chiefs of nephrology divisions at academic institutions, nephrology fellowship training program directors, patients and care partners, representatives from nephrology practices, ASN's committees, and leaders of kidney organizations. As mentioned previously this year in an April *Kidney News* article (1), conversations about required procedures or program requirements have been going on for many years. As such, the task force will focus on defining the big picture as it relates to the future of nephrology and then work backward into requirements for training, certification, and recertification.

"As we face a crisis in the nephrology workforce, now is the time to think big and strategically about the specialty's role in the broader health care system," said ASN Executive Vice President Tod Ibrahim. "Nephrologists care for some of the most complex patients, but the specialty is too often undervalued by the broader system."

To learn more about the task force and its charge, please refer to the article in the April issue of *Kidney News* (1). Regular updates will be provided in *Kidney News* through October 2022. To provide your thoughts and ideas on the future of nephrology, please email Melissa West, ASN's Senior Director for Strategic Relations and Patient Engagement, at mwest@asn-online.org.

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Detective Nephron

Detective Nephron, world-renowned for his expert analytic skills, trains budding physician-detectives in the diagnosis and treatment of kidney diseases. Mackenzie Ula Densa, a budding nephrologist, plans to present a new case to the master consultant.

Nephron It's been a while, Mac. What do you have for me?

Mac I have a 67-year-old man with a serum sodium (Na) of 120 mEq/L.

Nephron (*excited*) Whoa! Finally...electrolytes stuff!

Mac Trust me, you are going to love this one. You are like a child when it comes to hyponatremia.

Nephron Did you know that hyponatremia is the most searched item on UpToDate.com?

Mac Hmm…. I can totally relate to that.

Pause

Mac This man in his 60s has diabetes mellitus and a history of some form of autoimmune pancreatitis and…

Nephron Stop! Nice! What an amazing topic. Nephrologists love and hate hyponatremia. I think it is just fascinating. Is he symptomatic?

Mac (*laughing out loud*) No, not really. Interestingly, his kidney function is normal; his serum osmolality is 290 mOsm/kg.

Nephron (*angry*) Oh, come on! You are spoiling the fun! So, are you telling me this is not true hyponatremia?

Mac (*surprised*) I thought you love esoteric stuff! The way I categorize hyponatremia is based on serum osmolality. If the serum osmolality is <275 mOsm/kg, I would assume that this is true *hypotonic* hyponatremia. If it is >275 mOsm/kg, then we are dealing with three forms of *hyponatremias*: isotonic, hypertonic, or hypotonic hyponatremia.

Nephron (*bored, rolling his eyes*) Oh yes! You just nailed an important forgotten concept: Plasma tonicity does not equate to plasma osmolality. Excellent! Plasma osmolality refers to the concentration of the particles dissolved in plasma, whereas plasma tonicity refers to the concentration of particles that have an osmotic effect and are able to pull water (effective osmolality). These are solutes that cannot cross cell membranes and have predominantly extracellular fluid distribution.

Mac Well, let's get the easy side done first. If this was true hyponatremia—hence, hypotonic hyponatremia—then I would look at the urine, I think, in two buckets: urine osmolality high > 100 mOsm/kg or urine osmolality low ≤ 100 mOsm/kg.

Nephron (*winking*) I am glad you are thinking what the kidney is thinking! If you have hyponatremia with a low plasma tonicity, then the kidney is doing the appropriate thing when the urine osmolality is low or in the ≤100 bucket. In other words, the urine is appropriately diluted for the hypotonic plasma. The kidney is trying to rid the body of excess water to correct the hyponatremia by dumping it out into the urine. Is this vasopressin dependent or independent hyponatremia?

Mac Independent, of course…don't be ridiculous! In this case, vasopressin or the anti-diuretic hormone (ADH) is low. Thus, water is not reabsorbed in the tubules, leading to a dilute urine.

Nephron (*laughing*) This brings three diagnoses to mind: low solute intake, such as tea and toast; beer potomania and primary polydipsia; and in patients with reduced kidney function. Hyponatremia, due to low solute intake, seems to correct very fast, as most people tend not to recognize that diagnosis.

Mac Urine osmolality in this patient was 340 mOsm/kg; urine Na was...

Nephron But wait! Why? Why? Why? You don't need to go there yet. You had told me his serum osmolality was 290…

Mac (*trying to remember*) Oh yes. You are correct…

Nephron (*jumps in*) Let's go back to your categorizing the hypotonic hyponatremia and if the urine osmolality was >100 mOsm/kg. This is vasopressin dependent!

Mac (*surprised*) Obviously! The serum Na is low, indicating there is little excess water, and the kidney is retaining more water because vasopressin is signaling it to do so. Now, we need to figure out why.

Silence

Mac Hmm...you are exactly correct! What do you think about checking the urine Na?

Nephron (*shocked*) Yes! And if it is low (<20 mEq/L), then you are dealing with a condition where vasopressin secretion is physiologically appropriate and caused by low effective arterial blood volume. This could be in the setting of volume depletion, heart failure, or cirrhosis.

Mac (*jumps in*) And, if the urine Na is >30 mEq/L or so, then you have a vasopressin secretion that is physiologically inappropriate, and you are dealing with endocrine disorders, such as cortisol deficiency and everyone's favorite: syndrome of inappropriate anti-diuresis (SIAD). They keep changing names in nephrology! Oh well, no more syndrome of inappropriate ADH (SIADH). Some use it still, and some don't. What's in a name?

Nephron So, let's get back to our case. That was a nice discussion so far.

Mac (*confidently*) The patient in our case has a serum osmolality of 290. I would think this is pseudohyponatremia.

Nephron Hmmm…. Not all the time. Remember, you had mentioned earlier that this depends on the tonicity. You can still have hypotonic hyponatremia even when the serum osmolality is >275 mOsm/kg, caused by the presence of ineffective osmoles, such as ethanol or urea, which distribute freely across the cell membrane and increase the osmolality but not the tonicity. Therefore, sometimes, a person with alcohol use disorder can be hyponatremic and have a normal serum osmolality (remember tonicity is not equal to osmolality).

Mac (*confused*) Good point. But when you have high serum osmolality, it is possible that the tonicity is also high, as seen in hyperglycemia or mannitol.

Nephron (*interrupting*) Excellent point! But when the serum osmolality and the tonicity are normal, then you have this entire category of iso-osmolar isotonic hyponatremia that is seen with paraproteinemia and hyperlipidemias.

Mac Although our patient has diabetes, his serum glucose is not high. He has no history of hyperlipidemia or hypertriglyceridemia, and a recent paraprotein workup was negative. There are no elevated serum-free light chains.

Nephron Is this serum Na real? Did you repeat the lipids and serum-free light chains?

Mac (*nodding*) Yes, the serum-free kappa light was 4.3 mg/dL, and lambda was 3.5 mg/dL with a normal ratio for the serum creatinine of 0.9 mg/dL. Total cholesterol came back at 1900 mg/dL. His lipid panel, however, demonstrated a high-density lipoprotein (HDL) level of 39 mg/dL and triglycerides of 299 mg/dL. Electrolytes on a repeat blood sample were checked simultaneously using the indirect ion-selective electrode (ISE) method and the direct ISE method. The serum Na was 136 mEq/L in the direct ISE method and 119 in the indirect ISE method.

Nephron (*puzzled*) Fancy stuff you did there! I am glad you did not start the patient on oral urea or hypertonic saline. By the way, urea has become a new favorite for nephrologists, more than vaptans. But I see a rise in the sodium glucose co-transporter 2 inhibitor in this field soon. Let's wait. I have only seen the trailer…waiting for the movie!

Mac So dramatic, you are!

Nephron Hahaha! On a serious note, does this patient have jaundice?

Mac and Nephron exit to visit the patient bedside.

Nephron Mac, bedside rounds are the best! Brilliant! You don't even have to touch the patient anymore (only see that he is yellow and jaundiced). Physical examination reminders needed in electronic health records, please!

Mac (*confused*) Yes, apparently, he has a biliary stricture.

Nephron Fascinating information. Please order a lipoprotein electrophoresis stat.

Mac You know, that's probably a send-out test and likely not going to be stat.

Nephron (*jumps in*) Yes, of course. Tell your team to stop checking serum Na levels, and if low, ignore them.

A few days later

Mac (*surprised*) Well, his total cholesterol was in the 1900-mg/dL range. Triglycerides were 239, very low-density lipoprotein (VLDL) was 140s, and HDL was very low, at a 5 range. The LDL X came back at a 1700 range. That was a very high value.

Nephron Fantastic! Lipoprotein X...makes sense. That is an LDL with a presence in the serum that is extremely specific for cholestasis. Phospholipids and unesterified cholesterol constitute the bulk of this molecule. Its lipid composition is like lipids found in normal bile but differs significantly from normal plasma lipoproteins. In cholestasis, bile lipoprotein refluxes into the plasma pool and binds to albumin to form this lipoprotein X.

Mac Does resolution of cholestasis coincide with improvement in hypercholesterolemia in most cases?

Nephron Yes, of course! Remember, this was your classic "pseudohyponatremia." Truly not real.

Low plasma Na in the context of normal tonicity is an analytical measurement artifact observed with increases in the solid fraction of plasma. Osmolality, measured by freezing-point depression, is not affected by such changes. Indirect ISE methods use diluted specimens and calculate electrolyte concentrations using a fixed factor based on normal plasma water content. In specimens with an increased solid fraction, the measured result is accurate. However, because the fixed factor used is not appropriate, an error is introduced, causing falsely low calculated results. Because direct ISE measures electrolyte concentrations in undiluted specimens, results measured by this method are not subject to the same artifact.

Silence

Nephron The presence of lipoprotein X should be considered in patients with obstructive jaundice and hyponatremia, particularly when results from routine lipid panels are confusing. Some gastrointestinal cancers affecting the gallbladder, causing obstruction and jaundice, can also do this.

A few days later

Mac (*winking*)

Nephron Yes, clearance of the obstruction and cholestasis resolved the serum Na.

Mac (*with excitement*) Yes! Yes!

Nephron (*laughing*) There you go again! Fascinating diagnosis, and treatment was to do nothing. Do no harm first, my friend. Do no harm. Let's have some NY style coffee today…. ■

Detective Nephron was developed by Kenar D. Jhaveri, MD, Professor of Medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY. Thanks go to Rimda Wanchoo, MD, Professor of Medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, and Helbert Rondon, MD, Associate Professor of Medicine at the University of Pittsburgh Medical Center, PA, for their editorial assistance. Send correspondence regarding this section to kjhaveri@northwell.edu or kdj200@gmail.com.

Coffee Drinkers May Have Lower Acute Kidney Injury Risk

Drinking at least two cups of coffee per day has a protective effect against acute kidney injury (AKI), reports a study in *Kidney International Reports*.

The analysis included 14,207 adults, aged 45 to 64 years, from the population-based Atherosclerosis Risk in Communities (ARIC) study. Coffee consumption was assessed at a single study visit using a semiquantitative food-frequency questionnaire and was evaluated for association with incident AKI.

Of the participants, 27% never drank coffee, 14% drank less than one cup per day, 19% drank one cup per day, 23% drank two or three cups per day, and 17% drank more than three cups per day. Several of the following health factors were associated with higher coffee consumption: absence of diabetes, lower body mass index (BMI), lower systolic and diastolic blood pressure, and higher daily energy intake. Estimated glomerular filtration rate (eGFR) was slightly lower for participants who drank more coffee.

Associations of coffee consumption with lower risk of AKI were significant for two to three cups and for three or more cups per day. The trends remained significant after adjustment for age, sex, race, education, daily energy intake, physical activity, smoking, alcohol use, diet quality, systolic blood pressure, diabetes status, anti-hypertensive therapy, eGFR, and BMI.

Coffee is widely consumed worldwide and has been linked to a wide range of health benefits. In a previous ARIC analysis, higher coffee consumption was associated with a lower incidence of chronic kidney disease.

Although emphasizing the need for more research, the investigators conclude, "Our data support chronic coffee consumption as an opportunity for cardiorenal protection through diet, particularly for the prevention of AKI hospitalizations or procedures" [Tommerdahl KL, et al. Coffee consumption may mitigate the risk for acute kidney injury: Results from the Atherosclerosis Risk in Communities (ARIC) study. *Kidney Int Rep*, published online ahead of print May 5, 2022. https://www.sciencedirect.com/science/article/pii/S2468024922013699]. ■

MEET THE AMERICAN KIDNEY FUND'S 2022 CLINICAL SCIENTIST IN NEPHROLOGY PROGRAM FELLOWSHIP RECIPIENTS

The American Kidney Fund (AKF) has awarded its 2022 Clinical Scientist in Nephrology Program fellowships to two deserving researchers: Jillian Caldwell, DO, a nephrology fellow with Stanford University School of Medicine, and Janewit Wongboonsin, MD, MS, a clinical and research fellow with the Brigham and Women's Hospital (BWH)-Massachusetts General Hospital (MGH) Renal Fellowship Program, conducting his postdoctoral research at Boston Children's Hospital (BCH). *Kidney News* is honored to present an interview with these awardees.

Jillian Caldwell, DO

Fellowship project: How immunologic matching in kidney transplantation can affect equitable access to organs

Tell us about yourself and something unique about you.

I was born and raised in San Francisco, CA, but I've lived in a few different places: Montreal during my undergraduate degree at McGill University and then Chicago for medical school at Midwestern University and for residency at the University of Illinois Chicago. I moved back to the Bay Area to start my nephrology fellowship at Stanford School of Medicine after living elsewhere for 13 years, and I'm happy to be back. I will say that living through 13 cold winters in Canada and the Midwest turned me into an avid knitter, and I'm trying to keep that hobby up in my (limited) spare time during fellowship.

What brought you to the field of nephrology?

Physiology courses in medical school contributed to my interest in nephrology. Although most of my classmates dreaded the renal physiology section, I always loved it. It seemed that if you understood the physiology of the kidney, you could make sense of what was going on with your patients. I've never been very good at memorizing unless I understand the logical reasoning behind something, and nephrology is perfect for that kind of learner. I gained even more respect for nephrology after seeing the close relationship between nephrologists and their patients and how life-altering both dialysis and kidney transplantation can be.

What inspired you to apply for the AKF Clinical Scientist in Nephrology fellowship?

Several other phenomenal researchers in the Division of Nephrology at Stanford had previously received the AKF award—all very talented—and spoke highly of the opportunities they received as a result. After meeting my mentor, Dr. Xingxing Cheng, and brainstorming our project on immunologic matching in kidney transplantation, I was highly motivated to apply for this grant as a way to bring this project to life. The process of writing and revising the grant solidified my motivation to pursue a career in research and built a roadmap for me to follow when I begin the award period in July, and I'm so excited to do so!

Tell us about your project for AKF and why you chose it.

My project aims to look at how immunologic matching in kidney transplantation can affect equitable access to organs. Although immunologically matched kidney transplants demonstrate better outcomes in terms of patient and kidney survival, racial and ethnic minorities are less likely to receive fully matched kidneys, a disparity historically attributed to the genetic makeup of the donor pool. The aim is to identify the reason for this and to test alternative ways of allocating kidneys to account for the disparities. The motivation for this project comes from my experiences with patients who have lost kidney function after losing access to immunosuppression—frequently because of systemic barriers to health care that disproportionately affect racial and ethnic minority patients. I am motivated to examine disparities in access to transplantation and explore strategies that promote equity and efficiency within the system.

What does receiving the AKF Clinical Scientist in Nephrology fellowship mean to you?

This award will help me achieve my goals of becoming an academic nephrologist, in addition to providing networking opportunities and the ability to present my work at national conferences. I am honored and grateful to have been chosen for the award, which will further motivate me to do the best work possible.

What is your advice for younger colleagues and your hope for their future in nephrology?

My advice is to find a project that inspires you. Frustrating clinical scenarios—for me, seeing patients with barriers to health care—are a great inspiration for research work. Believing that your project is meaningful and directly impacts your patients should help you work through the challenges and obstacles inherent to any research project.

Janewit Wongboonsin, MD, MS

Fellowship project: Defining the prevalence of genomic forms of nephrotic syndrome in adults and their clinical impact

Tell us about yourself and something unique about you.

I was born in Bangkok, Thailand, and grew up there. I attended Mahidol University's Faculty of Medicine at the Siriraj Hospital in Bangkok for my medical degree. In my last year of medical school, I was one of the representatives of my school to compete for a 1-year research fellow scholarship from the Prince Mahidol Award Foundation and was one of the five selected students. I was fortunate to join Dr. Benjamin Humphreys' lab in the renal division of BWH in Boston, MA, and then at Washington University School of Medicine in St. Louis, MO, for a total of 2 years, conducting kidney stem cell and fibrosis research. I am currently undertaking my postdoctoral research at BCH. One fun fact about me is that during my 5th year in medical school, I was a moderator for "Kid Vit Kids Sci," a Thai PBS television program about science.

What brought you to the field of nephrology?

When I competed for the Prince Mahidol Award Youth Scholarship in my last year of medical school, I was to select a subspecialty in which to pursue my research. The inspiration for me to study kidney stem cells started when I learned that Thailand provided universal coverage for renal replacement therapy. I realized how high the cost of care for patients with kidney diseases is, and I wanted to help slow or reverse kidney disease progression. By joining Dr. Humphreys' lab, it has broadened my horizon on the science and technology of nephrology. I was fascinated by both the pathophysiology and molecular mechanism of kidney diseases. After my first renal elective rotation at the University of Minnesota in Minneapolis, where I did my residency, I appreciated the breadth and depth of kidney diseases, and the mentorship and support I received have encouraged me to choose nephrology as my career.

What inspired you to apply for the AKF Clinical Scientist in Nephrology fellowship?

During my renal fellowship interview period, I had the opportunity to meet Dr. Matthew Sampson from BCH. I was excited to learn about how to use genomics and multi-omics to solve various kidney problems ("kidneyomics"), and I felt that I could thrive in an academic career under his mentorship. Furthermore, as a trainee on a visa, there are limited grant opportunities to support a career in research, and this award will allow me to follow this path. Additionally, several renal attendings in my fellowship who have received this award have been fantastic role models in research and clinical care, as I strive to be.

Tell us about your project for AKF and why you chose it.

My project will define the prevalence of genomic forms of nephrotic syndrome in adults and their clinical impact. The Mass General Brigham Biobank, which has enrolled more than 130,000 adult patients across its health care system, linking their electronic health records with genomic data generated for research, provides a powerful opportunity to pursue this study. Genomic information has shown promise in assisting with diagnosing and managing kidney diseases. However, there is more to learn to enable the translation of genomic technology to genomic medicine. I chose this project because it has become evident to me during my clinical nephrology training how genetic information could illuminate understanding patients' conditions in various scenarios and impact their care.

What does receiving the AKF Clinical Scientist in Nephrology fellowship mean to you?

This fellowship award means that I will be able to have dedicated research time for up to 2 years. Not only can I pursue the aim of the research—to understand the impact of genetic data in patients with nephrotic syndrome—but also, this fellowship will allow me to develop expertise in clinical renal genetics, which may become another renal subspeciality. I will have the opportunity to collaborate and learn from the genomic community in Boston across multiple institutions, including BWH, MGH, BCH, and the Broad Institute. I will be able to join the ClinGen Kidney Disease Working Group expert panel to review gene-disease relationships and participate in the variant interpretation of various kidney conditions. These opportunities would be hard to achieve without the grant support from AKF.

What is your advice for younger colleagues and your hope for their future in nephrology?

One significant change that boosted my career in nephrology was joining KIDNEYcon in

Little Rock, AR, in 2018. I had the opportunity to meet with prominent leaders in the field. I received a lot of good advice that opened the door to many educational resources. I think nephrology has been ahead of many specialties in democratizing education. I like to learn the exciting, new concepts in nephrology, and now these are not limited to just one institution. I benefited from my supportive nephrology program and the global education community to gradually craft my interest in renal genetics. I would encourage future trainees to try out different areas of interest. It isn't easy to prospectively guess how your career will develop, but it will always be fulfilling when you connect the dots. ■

Commentary

The Kidney Community's and Renal Physician Association's Role in Valuing Nephrologists' Work

By Adam Weinstein and Eileen Brewer

Health care providers eagerly anticipate the Centers for Medicare & Medicaid Services (CMS) updates to the physician fee schedule (PFS) in the *Federal Register* each fall. The PFS, which assigns relative value units (RVUs) to Current Procedural Terminology (CPT) codes, is CMS's price list for physician services. The published CPT values result from thousands of hours of work by specialty society representatives (called advisors) and the 32 members of the American Medical Association (AMA)/Specialty Society Relative Value Scale Update Committee (RUC) (1).

Per AMA bylaws, specialty societies that meet requirements for representation in the AMA House of Delegates may appoint representatives to the RUC. For the last 30 years, the Renal Physicians Association (RPA) has qualified to have RUC advisors advocating for the value of nephrology-related CPT codes (2). RVUs are the basis of most physician payments, including employment contracts and parts of value-based care programs, such as the Chronic Kidney Disease Quarterly Capitated Payment (CKD QCP) in the Comprehensive Kidney Care Contracting (CKCC) model.

Before establishing the relative value system, CMS paid physicians at "usual and customary" rates, which proved to be fiscally untenable. In 1989, Congress mandated the use of the Harvard resource-based relative value scale (RBRVS) study methodology for all Medicare payments (3). Establishing a work- and intensity-based relative value for every medical procedure (from removing a glioblastoma to providing psychotherapy) proved complex and led in 1991 to regular RUC meetings at which AMA-participating medical society RUC advisors present typical physician work and practice expense RVUs to the 32 members of the RUC through a fair and structured methodology (4). A 2011 study, the most recent peer-reviewed article on this topic, found that CMS, on average, accepts 85%–95% of CPT values recommended by the RUC (1).

As seen in Figure 1, both new and existing CPT codes are referred for RUC review. Societies representing specialties that most frequently submit bills for the reviewed CPT code are expected to survey their members to establish typical physician work RVUs and practice expense values to ensure appropriate relativity compared with similar CPT codes.

The RUC holds triannual meetings, where specialty society advisors present survey findings and recommend CPT valuation, defending their recommendations with survey data and precedent valuations of similar RUC-reviewed CPT codes. After each meeting, the RUC sends its recommendations for work RVUs and practice expenses to CMS for internal deliberation, finalization, or further alteration before inclusion in the PFS. The RUC may recommend 200–400 CPT code values to CMS in a typical year.

Among the 32 members of the RUC, there are six AMA representatives, 22 permanent specialty society seats, and four rotating seats for 2-year, non-repeating terms. Two of the rotating seats are for internal medicine subspecialties, one is for primary care, and one is for any specialty (5). Specialty society-nominated physician candidates for the rotating seat are elected by RUC members. Nephrologists who are members of RPA were elected to an internal medicine rotating seat in 2014 and 2022.

Although far from perfect, the RUC process influences how most CPT codes obtain absolute and relative values in the United States. Having physicians experienced in the RUC process and with backgrounds in CPT coding who establish and agree on these values is critical (6, 7). RPA's RUC advisors have defended multiple CPT code values, including establishing values for 90950–90970 in 2008 and various interventional nephrology procedures in recent years. Nephrologists can participate in several ways:

1. Maintain both RPA and AMA membership. RPA relies on having at least 20% of its members maintain AMA membership to be a voice for nephrology at the RUC.
2. Participate in RPA member surveys to establish a CPT code's typical time, work, intensity, and practice expense. Review and respond appropriately to any email from RPA titled "RUC Survey."
3. Review the AMA literature on the relative value system.

The lingua franca of physician work in the American medical system is the RVU. All physicians must think about our time and effort in these terms, as it is the best means to ensure a robust workforce to care for our patients. ■

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Dr. Weinstein is a full-time employee of DaVita and reports no conflicts with the information presented in this article. Dr. Brewer reports no conflicts of interest.

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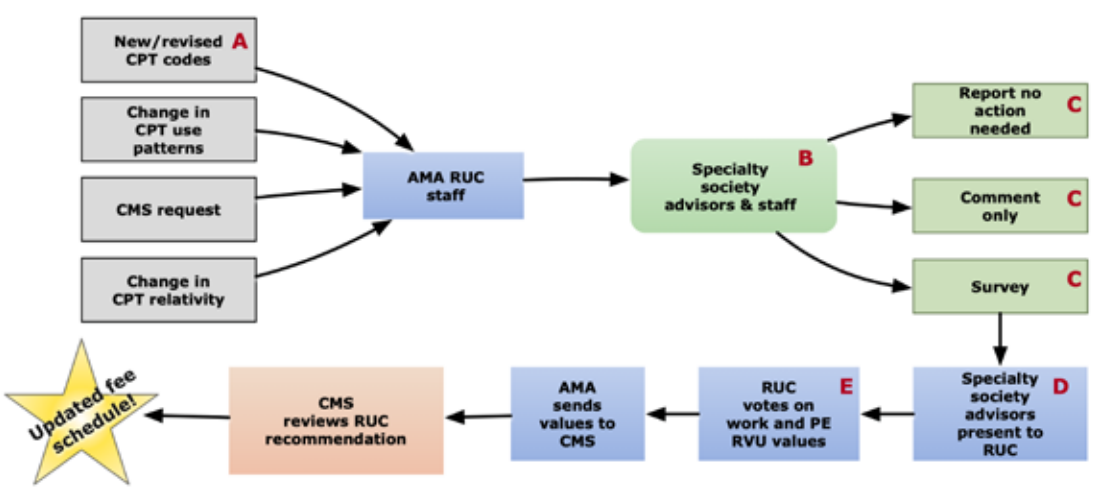
Figure 1. Steps in the CPT valuation process and RPA participation



(A) RPA nephrologists participate in the AMA CPT committee. (B) RPA's CPT/RUC workgroup, which includes RPA's RUC advisors, works with AMA staff to ensure nephrology is represented in any codes requiring review. (C) RPA's CPT/RUC workgroup will respond to any nephrology-related CPT valuation requests and send surveys to RPA membership if needed. (D) RPA's advisors represent nephrology to the RUC. (E) RPA nephrologists have been elected to rotating seats on the RUC in 2014 and 2022. PE, practice expense.

Cardiometabolic Consequences of Long COVID

By Evan Xu and Ziyad Al-Aly

Beyond its acute effects, it is now compellingly clear that infection with SARS-CoV-2 leads to serious long-term health consequences—referred to as long COVID. Of particular concern is the increased risk of cardiometabolic disease, including kidney diseases, diabetes, and cardiovascular disease (Figure 1).

In the first large-scale, high-dimensional characterization of the post-acute sequelae of COVID-19, we showed that people who survive the acute phase of COVID-19 have increased risk of post-acute sequelae involving pulmonary and a wide array of extrapulmonary disorders (1).

Further work from our team revealed that people who survive the acute phase of COVID-19 have an increased risk of developing kidney events in the post-acute phase of the disease, including acute kidney injury, decline in estimated glomerular filtration rate (eGFR), chronic kidney disease, and end stage kidney disease (2). In other work involving a comprehensive assessment of post-acute sequelae in the cardiovascular system at 1 year, we showed that people with COVID-19 were at an increased risk for developing cerebrovascular disease, dysrhythmias, inflammatory heart disease, ischemic heart disease, thrombotic disorders, and major adverse cardiac events (a composite risk of all-cause mortality, stroke, and myocardial infarction) (3). Most recently, we showed that after 1 year of follow-up, people with COVID-19 had a significantly higher risk of diabetes than non-infected controls (4). In all these analyses, the risk of post-acute sequelae was evident even in people whose acute COVID-19 was mild and did not necessitate hospitalization; these people represent the majority of those with COVID-19. There was also a graded increase in risk according to the severity of the acute infection, which progressively increased from non-hospitalized to hospitalized to admitted to intensive care (1–4).

The burden of cardiometabolic conditions is significant. We estimate that the absolute burden of these conditions ranges from 1% to 4% of people with COVID-19. Given the large number of people impacted with COVID-19, these single-digit percentages will translate into millions of affected people in the United States and many more around the world. This will likely have far- and wide-reaching ramifications on almost every aspect of our lives. It will drive an increase in burden of non-communicable diseases, impact health care costs, lead to a decline in life expectancy, and adversely affect labor participation and economic productivity and may have global-security implications.

Long after the pandemic abates, millions of people will still bear its scars in the form of cardiometabolic disease (and other facets of long COVID). People with cardiometabolic disease due to COVID-19 will need post-COVID-19 care. Governments and health systems around the world must be prepared to meet the challenges posed by the long-term consequences of the COVID-19 pandemic. This will entail, among other things, building health system capacity and care pathways to equitably address the care needs of people with long COVID and its myriad manifestations. ■

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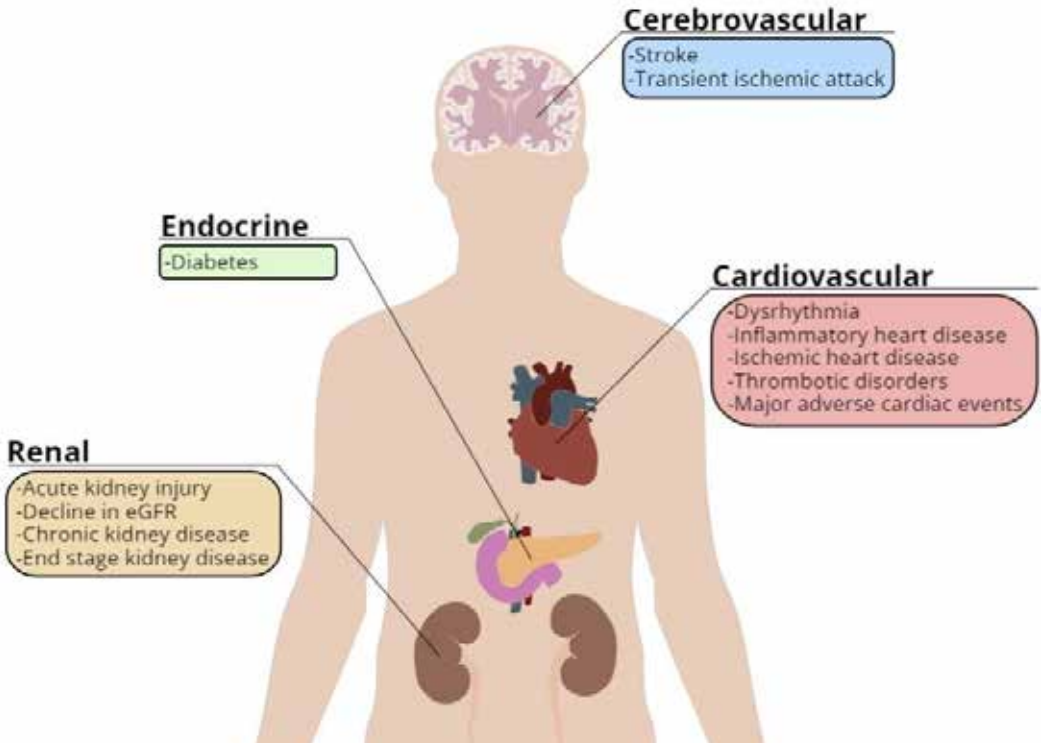
The authors report no conflicts of interest.

Figure 1. Cardiometabolic consequences of long COVID



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