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Nephrology Fellowship Recommendations Emphasize Competency-Based, Individualized Training

By Bridget M. Kuehn

New recommendations from the ASN Task Force on the Future of Nephrology emphasize 2 years of competency-focused training with individualized training in both the second 12 months of fellowship as well as a third year for specialized careers.

ASN established the task force in April 2022 in response to requests from the American Board of Internal Medicine (ABIM) and the Accreditation Council for Graduate Medical Education (ACGME) to update nephrology training requirements. The team created five nephrology fellowship-specific recommendations emphasizing competency-based and individualized training and five more general recommendations focusing on topics ranging from improving fellow wellness to combating health inequity. The task force submitted its recommendation to ABIM and ACGME on November 11 and published the report (1) to engage the ASN community on the next step of implementation.

"It is going to take many years to work through the details of this plan," said Task Force Chair Mark Rosenberg, MD, professor of medicine in the Division of Nephrology and Hypertension at the University of Minnesota in Minneapolis, during a session at Kidney Week 2022 introducing the recommendations. "This is a real opportunity to engage our community and [its] expertise in trying to define these levels of competency."

Competency-based

The fellowship-specific recommendations call for nephrology to adopt a competency-based training model like that of the American College of Cardiology's Core Cardiology Training Symposium.

The first recommendation focuses on establishing three levels of competency. The first level of competency would focus on core skills, values, attitudes, and knowledge that every nephrologist needs, similar to the first 12 months of current fellowship training. The second level would focus on experience with advanced procedures and patient care. Fellows could achieve the first two competency levels in a standard 2-year fellowship program. More individualized training to meet fellows' individual career goals could begin in the second year and potentially stretch into an optional third year. For example, a third-year program may focus on kidney transplant or nephrology procedures, Rosenberg explained.

The second recommendation calls for fellowship pro-

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Patient-Care Innovations, ICU Alerts Show Promise in Trials

By Bridget M. Kuehn

Many late-breaking clinical trials presented at Kidney Week 2022 demonstrated innovative approaches to improving kidney care. Trials showed ways to incorporate coaching and health education and to provide more kidney-safe care during transplant or intensive care unit (ICU) admission, challenged the benefits of cold dialysate, and tested cutting-edge immunoglobulin A (IgA) nephropathy treatments.

Kidney health inequities

Many Black Americans may face substantial barriers to heart- and kidney-healthy diets owing to socioeconomic constraints, a void in nutrition information, or living in food deserts. However, a study presented by Deidra Crews, MD, ScM, professor and deputy director of the Johns Hopkins Center for Health Equity in Baltimore, MD, showed that coaching paired with subsidies for healthy food might help Black individuals with kidney diseases overcome these barriers. Crews presented the study results during the High-Impact Clinical Trials session at Kidney Week 2022.

Crews and her colleagues randomly assigned 142 Black adults with hypertension and chronic kidney disease (CKD) to receive a $30 grocery gift card weekly for 4 months, with or without coaching about high-potassium foods and how to follow the Dietary Approaches to Stop Hypertension (DASH) diet. The group without coaching received a brief

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Inside

NEW FDA-APPROVED DATA

KRYSTEXXA **can change the course** of uncontrolled gout[1]

KRYSTEXXA with methotrexate:

>80%
relative improvement in patient response;
71% (71/100) vs 39% (20/52) complete response* compared to KRYSTEXXA alone[1]

87%
relative reduction in infusion reactions;
4% (4/96) vs 31% (15/49) compared to KRYSTEXXA alone[1]

A 52-week, randomized, double-blind trial conducted in adult patients with chronic gout refractory to conventional therapy to evaluate administration of KRYSTEXXA 8 mg Q2W co-administered with 15 mg oral methotrexate QW and 1 mg oral folic acid QD vs KRYSTEXXA alone.[1,2]

QD, every day; QW, every week; Q2W, every 2 weeks.

*Complete sUA response: The primary efficacy endpoint was the proportion of responders, defined by patients achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 6.[1]

INDICATION

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.

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

IMPORTANT SAFETY 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. Delayed hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Premedicate with antihistamines and corticosteroids and closely monitor for anaphylaxis for an appropriate period after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to each infusion and discontinue 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 glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. KRYSTEXXA is contraindicated in patients with G6PD deficiency.**

CONTRAINDICATIONS:

- In patients with G6PD deficiency.
- In patients with history of serious hypersensitivity reactions, including anaphylaxis, to KRYSTEXXA or any of its components.

Dissolve years of systemic urate deposition[3]
ChangeTheCourse.com

WARNINGS AND PRECAUTIONS

Gout Flares: An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including KRYSTEXXA. 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 formally studied in patients with congestive heart failure, but some patients in the pre-marketing placebo-controlled clinical trials experienced exacerbation. Exercise caution in patients who have congestive heart failure and monitor patients closely following infusion.

ADVERSE REACTIONS

The most commonly reported adverse reactions (≥5%) are:

KRYSTEXXA co-administration with methotrexate trial:
KRYSTEXXA with methotrexate: gout flares, arthralgia, COVID-19, nausea, and fatigue; KRYSTEXXA alone: gout flares, arthralgia, COVID-19, nausea, fatigue, infusion reaction, pain in extremity, hypertension, and vomiting.

KRYSTEXXA pre-marketing placebo-controlled trials:
gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis, and vomiting.

Please see Brief Summary of Prescribing Information for KRYSTEXXA on following page.

References: 1. KRYSTEXXA (pegloticase) [prescribing information] Horizon. **2.** Botson J, et al. *J Clin Rheumatol*. 2022;28:e129-e134. **3.** Data on File. Horizon, March 2022.

HORIZON.

KRYSTEXXA®
pegloticase

KRYSTEXXA® (pegloticase) injection, for intravenous use

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

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

See full prescribing information for complete boxed warning.

- **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 hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Pre-medicate with antihistamines and corticosteroids and closely monitor for anaphylaxis for an appropriate period of time after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to each infusion and discontinue 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. KRYSTEXXA is contraindicated in patients with G6PD deficiency.**

INDICATIONS AND USAGE

KRYSTEXXA® (pegloticase) is 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.

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

CONTRAINDICATIONS

KRYSTEXXA is contraindicated in:

- Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency *[see Warnings and Precautions]*
- Patients with history of serious hypersensitivity reactions, including anaphylaxis, to KRYSTEXXA or any of its components

WARNINGS AND PRECAUTIONS

Anaphylaxis

In a 52-week controlled trial, which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, patients were pre-treated with standardized infusion reaction prophylaxis and were discontinued from treatment with KRYSTEXXA if serum uric acid levels increased to above 6 mg/dL at 2 consecutive visits after the initiation of KRYSTEXXA therapy to reduce the risk of anaphylaxis. One patient randomized to the group treated with KRYSTEXXA co-administered with methotrexate (1%) experienced anaphylaxis during the first infusion and no patients experienced anaphylaxis in the group treated with KRYSTEXXA alone *[see Adverse Reactions]*.

During pre-marketing clinical trials with KRYSTEXXA alone, KRYSTEXXA was not discontinued following 2 consecutive serum uric acid levels above 6 mg/dL. 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, nausea or vomiting. 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 discontinue 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

In a 52-week, controlled trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone *[see Adverse Reactions]*, patients were pre-treated with standardized infusion reaction prophylaxis and were discontinued from treatment with KRYSTEXXA if serum uric acid levels increased to above 6 mg/dL at 2 consecutive visits after the initiation of KRYSTEXXA therapy to reduce the risk of infusion reactions. Infusion reactions were reported in 4% of patients in the KRYSTEXXA co-administered with methotrexate group compared to 31% of patients treated with KRYSTEXXA alone experienced infusion reactions *[see Adverse Reactions]*. In both treatment groups, the majority of infusion reactions occurred at the first or second KRYSTEXXA infusion and during the time of infusion. Manifestations of these infusion reactions were similar to that observed in the pre-marketing trials.

During pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, KRYSTEXXA was not discontinued following 2 consecutive serum uric acid levels above 6 mg/dL. 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 discontinue 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

In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, patients were administered gout flare prophylaxis similar to that in the pre-marketing, placebo-controlled trials.

In this trial, the percentages of patients with any flare for the first 3 months were 66% and 69% for the group treated with KRYSTEXXA co-administered with methotrexate and the group treated with KRYSTEXXA alone, respectively. In the group treated with KRYSTEXXA co-administered with methotrexate, the percentages of patients with any flare for the subsequent 3 month increments of treatment were 27% during Month 6, 8% during Month 9 and 9% during Month 12. In the group treated with KRYSTEXXA alone, the percentages of patients with any flare were 14% during Month 6, 9% during Month 9 and 21% during Month 12.

During pre-marketing, 24-week controlled clinical trials with KRYSTEXXA alone, 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 *[see Dosage and Administration]*.

Congestive Heart Failure

KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the pre-marketing, 24-week controlled clinical trials experienced exacerbation of congestive heart failure. 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 *[see Adverse Reactions]*.

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

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.

Co-administration with Methotrexate

A 52-week, randomized, double-blind trial was conducted in adult patients with chronic gout refractory to conventional therapy to evaluate administration of KRYSTEXXA 8 mg every 2 weeks co-administered with weekly administration of oral methotrexate 15 mg, compared to KRYSTEXXA alone. In this trial, patients who were able to tolerate two weeks on methotrexate 15 mg were then randomized to receive four additional weeks on either methotrexate 15 mg or matching placebo prior to initiating KRYSTEXXA therapy. A total of 152 subjects were randomized, and of these, 145 subjects completed the 4-week methotrexate run-in period and received KRYSTEXXA (96 subjects received KRYSTEXXA co-administered with methotrexate and 49 received KRYSTEXXA plus placebo) during the treatment period. All patients received pre-treatment with an oral antihistamine, intravenous corticosteroid and acetaminophen. These patients were between the ages of 24 and 83 years (average 55 years); 135 patients were male and 17 and were female; 105 patients were White/Caucasian, 22 were Black/African American,

14 were Asian, 5 were Native Hawaiian/Other Pacific Islander and 5 identified as Other; 28 were Hispanic or Latino. Common co-morbid conditions among the enrolled patients included hypertension (63%), osteoarthritis (25%), hyperlipidemia (24%), gastroesophageal reflux disease (22%), obesity (20%), type 2 diabetes (18%) and depression (16%). Patients with an eGFR <40 mL/min/1.73 m² were excluded from this trial.

The most commonly reported adverse reaction during the methotrexate pre-treatment periods was gout flare. The most commonly reported adverse reactions that occurred in ≥ 5% in either treatment group during the KRYSTEXXA co-administered with methotrexate or KRYSTEXXA alone period are provided in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients in Either the KRYSTEXXA Co-administered with Methotrexate or KRYSTEXXA Alone Treatment Period

Adverse Reaction	KRYSTEXXA with Methotrexate (N=96) n (%)	KRYSTEXXA Alone (N=49) n (%)
Gout flare	64 (67%)	35 (71%)
Arthralgia	13 (14%)	5 (10%)
COVID-19	9 (9%)	3 (6%)
Nausea	5 (5%)	6 (12%)
Fatigue	5 (5%)	2 (4%)
Infusion reaction	4 (4%)[a]	15 (31%)
Pain in extremity	1 (1%)	3 (6%)
Hypertension	1 (1%)	3 (6%)
Vomiting	0	4 (8%)

[a] Included one case of anaphylaxis

KRYSTEXXA ALONE

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 24-week 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. These patients were between the ages of 23 and 89 years (average 55 years); 173 patients were male and 39 were female; and 143 patients were White/Caucasian, 27 were Black/African American, 24 were Hispanic/Latino and 18 were all other ethnicities. Common co-morbid conditions among the enrolled patients included hypertension (72%), dyslipidemia (49%), chronic kidney disease (28%), diabetes (24%), coronary artery disease (18%), arrhythmia (16%), and cardiac failure/left ventricular dysfunction (12%).

During the pre-marketing placebo-controlled clinical trials, the most commonly reported adverse reactions that occurred in greater than or equal to 5% of patients treated with KRYSTEXXA 8 mg every 2 weeks are provided in Table 2.

Table 2. Adverse Reactions Occurring in 5% or More of Patients Treated with KRYSTEXXA Compared to Placebo

Adverse Reaction	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

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.

In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, approximately 26% of patients had pre-existing antibodies to pegloticase. Patients with an increase in titer from baseline or who were negative at baseline and developed an anti-pegloticase response at one or more post dose time points was 30% and 51%, for the KRYSTEXXA co-administered with methotrexate and KRYSTEXXA alone treatment groups, respectively. Patients with higher antibody titers were more likely to have faster clearance and lower efficacy.

During pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, 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.

Postmarketing Experience

The following adverse reactions 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.

General disorders and administration site conditions: asthenia, malaise, peripheral swelling

DRUG INTERACTIONS

Methotrexate

KRYSTEXXA 8 mg every 2 weeks has been studied in patients with chronic gout refractory to conventional therapy taking concomitant oral methotrexate 15 mg weekly. Co-administration of methotrexate with KRYSTEXXA may increase pegloticase concentration compared to KRYSTEXXA alone.

PEGylated products

Because anti-pegloticase antibodies appear to bind to the PEG portion of the drug, there may be potential for binding with other PEGylated products. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

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 *[see Data]*.

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. In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, 85% of patients had chronic kidney disease based on estimated glomerular filtration rate (eGFR) of ≥ 40 to < 90 mL/min/1.73 m² at baseline. In the pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, 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).

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, nausea or vomiting.
- 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 *[see Warnings and Precautions, Adverse Reactions]*
- 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 *[see Warnings and Precautions, Contraindications]*.

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 *[see Warnings and Precautions, Adverse Reactions]*. Advise patients that they should not stop KRYSTEXXA therapy if they have a flare.

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Reimagined Nephrology Fellowship Recommendations

Continued from cover

grams to create more individualized pathways to meet individual career goals. Programs could offer specialized training in subspecialties, such as kidney disease prevention, hypertension management, onconephrology, or palliative care. Programs might also include training in business or leadership, medical education, or research. "This recommendation will provide an opportunity for fellowship programs to distinguish themselves and to market some of the specialized areas of expertise," Rosenberg said.

The third recommendation calls for a greater emphasis on personalized care in alignment with the goals of the Advancing American Kidney Health initiative, which focuses on earlier diagnosis and prevention, prioritizing transplants, and giving patients treatment options, such as home dialysis.

The fourth and most controversial recommendation, according to Rosenberg, addresses expectations for fellows' procedural competency. The proposal calls for fellows to be knowledgeable about the procedures, their indications, and potential complications and to be able to advise patients about their options. However, it does not require competency in the procedures themselves. Programs are encouraged to provide opportunities in-house or offer external options for fellows who wish to pursue training in vascular access placement or kidney biopsies.

Rosenberg said the recommendation better reflects the realities of current nephrology practice in which most nephrologists either never perform these procedures or rarely do. Task force member Benjamin Humphreys, MD, PhD, the Joseph Friedman Professor of Renal Diseases in Medicine and chief of the Division of Nephrology at Washington University School of Medicine in St. Louis, MO, said that he initially was against the change. However, he was swayed by learning that many program directors felt forced into an ethical conundrum of certifying fellows as procedurally competent when many fellows do not feel competent. "The train has left the station already in terms of the reality of our workforce," Humphreys said.

Patient safety is another primary consideration, said task force member Suneel Udani, MD, consulting physician at Nephrology Associates of Northern Illinois and Indiana (NANI) Research, in Oak Brook, IL, who said the task force wanted to ensure that every fellow certified to do these procedures is doing them as safely as possible.

The fifth recommendation is to identify and close gaps in nephrology training. Rosenberg said this might include training in patient-centered care and patient engagement, addressing health disparities, regulatory aspects of kidney care, or the financial operations of a nephrology practice. Task force member Sharon Anderson, MD, professor and dean emeritus, Division of Nephrology & Hypertension, at Oregon Health & Science University in Portland, also noted the gaps in training for home dialysis and transplant care and recommended more systematic analysis of training gaps in the field. "This is important for nephrology to do on a regular basis, where we take a deep look at ourselves at how we're practicing," Anderson said.

Wellness and justice

The second set of recommendations requires collaboration between nephrologists and the broader health care system. These recommendations include improving fellow wellness; prioritizing diversity, equity, inclusion, and health care justice; ensuring equal opportunities for all nephrologists; fostering interprofessional and interdisciplinary practice; and promoting lifelong learning. "Promoting the well-being of fellows is a patient-safety issue," Rosenberg said. "It's a quality-of-care issue."

Improving the wellness of nephrology fellows may also help improve recruitment to the field when there is intense competition, said task force member Robert Hoover, Jr., MD, chief of the Section of Nephrology and Hypertension at Tulane University in New Orleans, LA. He said his program has successfully boosted recruitment by emphasizing measures to improve fellow wellness. For example, the program created a night float service to prevent fellows from having to respond to a call overnight and then work in the morning. Hoover's program also gives fellows an extra half day off each month. He emphasized the need for a program to protect fellows' time to learn and faculty's time to teach.

The task force's report emphasizes the urgent need to address the disproportionate burden of kidney diseases on people who are Black, Hispanic, Native American, Native Hawaiian or other Pacific Islanders, or Asian American. "We as a community have to have a laser focus on health equity," said task force member Janis Orlowski, MD, a nephrologist and chief health care officer at the Association of American Medical Colleges in Washington, DC.

The recommendations also emphasize the need for equal opportunities for nephrologists who graduated from an allopathic or osteopathic training program or who are international medical graduates. For example, the task force's report notes that one-half of nephrologists and 70% of nephrology fellows are international medical graduates. "More and more of our fellows are DOs [doctor of osteopathic medicine] and international medical graduates," Rosenberg said. The report emphasizes the need to support the success of the joint accreditation program created in June by ACGME, the American Osteopathic Association, and the American Association of Colleges of Osteopathic Medicine (2) and address barriers associated with the US visa program.

ASN is collecting feedback from members about the recommendations and will work with program directors at fellowship programs to help them get the necessary time, resources, and support to implement the changes. "We are here to support you," said Melissa West, senior director for strategic relations and patient engagement with the ASN Alliance for Kidney Health. ■

Recommendations of the ASN Task Force on the Future of Nephrology

The ASN Task Force on the Future of Nephrology has issued 10 recommendations for reimagining nephrology training. The first five focus on nephrology training:

1. Enhance competency-based nephrology education.
2. Establish individualized pathways to meet career goals.
3. Emphasize personalized care.
4. Reconsider expectations for training in procedures.
5. Close gaps in current nephrology training.

The second five recommendations are broader and require collaboration with the wider health care system:

6. Promote the well-being of nephrology fellows.
7. Prioritize diversity, equity, inclusion, and health care justice.
8. Ensure equal opportunities for all nephrologists.
9. Foster interprofessional and interdisciplinary practice.
10. Inspire lifelong learning.

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Patient-Care Innovations

Continued from cover

overview of DASH and a brochure at the start of the study. A dietician coached the other group about using their gift card to purchase high-potassium foods online for home delivery.

Crews and the 5PLUS Nuts + Beans for Kidneys investigators (1) followed the participants for 8 months after the gift cards stopped being provided, and participants in the coaching group continued to receive telephone-based coaching during that period. The coached participants increased dietary potassium intake and fruit and vegetable consumption. Individuals with a very high urine albumin-to-creatinine ratio (UACR) at baseline had a 73% decrease with coaching compared with a 21% increase among those without coaching. Patients with diabetes also saw greater benefits from coaching.

"Future dietary interventions that incorporate coaching or health education along with healthy food provision may better address kidney health inequities," Crews said.

Asked by attendee Don Wesson, MD, MBA, professor of medicine at Texas A&M College of Medicine in Dallas, how sustainable the intervention was, Crews responded that health systems or the supplemental food assistance program might implement the approach to help patients with hypertension and CKD who are food insecure.

Kidney-safe care

Results from the Better Evidence for Selecting Transplant Fluids (BEST-Fluids) trial (2) suggest that a balanced low-chloride crystalloid solution, called Plasma-Lyte 148, may be a better alternative to saline during a kidney transplant.

The trial randomized approximately 800 patients undergoing transplant to either saline or Plasma-Lyte 148 intravenous (IV) fluids during and after transplant surgery. Approximately 39% of patients in the saline group needed dialysis after surgery compared with only 30% in the Plasma-Lyte 148 group. The trial's co-principal investigator Michael Collins, MBChB, PhD, a senior consultant nephrologist at the Royal Adelaide Hospital, Australia, presented the results and said the number needed to treat with Plasma-Lyte 148 to prevent one case of delayed graft function was 10. There were similar rates of hyperkalemia in the two groups and no significant differences in rejection, graft failure, or death for up to 52 weeks post-surgery.

"These findings suggest that balanced crystalloids should be the standard IV fluid in deceased donor transplantation," Collins said. "This simple change in kidney transplant practice can be easily implemented globally, now."

During the question-and-answer session following the presentation, attendee Richard Lafayette, MD, professor

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Patient-Care Innovations

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in the Division of Nephrology at Stanford University, CA, agreed that this would be an easy switch. However, he raised concerns about why the study saw an immediate benefit in the Plasma-Lyte 148 group and why studies using balanced IV solutions have not shown a similar benefit in patients with acute kidney injury (AKI) in the ICU. Collins responded that his study's results are consistent with the SALT-ED (3) and SMART (4) studies and that patients in many trials in the ICU may have received saline before being randomized to an alternate IV fluid.

Nephrotoxic drug alerts

In other work (5) presented during the High-Impact Clinical Trials session, investigators found that automatic alerts to discontinue some nephrotoxic drugs given to patients in the ICU may improve patient outcomes.

F. Perry Wilson, MD, MSCE, and colleagues conducted an open-label, parallel-group trial to test the alerts at four US hospitals between August 2020 and November 2021. Wilson is associate professor and director of the Clinical and Translational Research Accelerator at Yale School of Medicine, New Haven, CT.

Approximately 5000 patients in the ICU with clinical signs of AKI, whose physicians were ordering non-steroidal anti-inflammatory drugs, renin-angiotensin-aldosterone system inhibitors, and proton pump inhibitors (PPIs), participated in the trial. Clinicians discontinued potentially nephrotoxic medications in 61.1% of patients after receiving an electronic pop-up at order entry alerting them to the patient's AKI. Clinicians who did not receive the pop-up discontinued potentially nephrotoxic medications for 55.9% of the patients in the control group. The difference between the groups was not statistically significant overall. However, there was a statistically significant increase in PPI discontinuation. The researchers did not see any safety signals associated with the alerts.

"Automated alerts for AKI can increase the rate of cessation of potentially nephrotoxic medications without endangering patients," Wilson said.

"That was a very nice study showing how we can leverage the power of the electronic medical record," said panel moderator Karen Griffin, MD, professor of medicine at Loyola University Medical Center in Chicago, IL, and Renal Section chief at the Edward Hines Jr. Veterans Affairs Hospital in Maywood, IL. "But as a practicing physician, I fear the potential of more alerts because of alert fatigue."

Griffin questioned whether targeted clinician education about the kidney risks of PPIs would be better. Wilson said that trials could help reduce the number of alerts by weeding out ineffective warnings. He and his team are currently testing whether sending the alerts to a dedicated team of clinicians who could provide more nuanced recommendations to the ordering clinician would be beneficial.

Cold dialysate debate

Cold dialysate did not reduce cardiovascular deaths or hospital admission compared with standard temperature dialysate, according to results of a massive dialysis center-based randomized trial (6) in Ontario, Canada. It also made patients uncomfortably cold.

The open-label MyTEMP trial randomized 84 Ontario hemodialysis centers to use dialysate cooled to 0.5°C below the patient's body temperature or standard temperature dialysate at 36.5°C. Over 4 years, more than 15,000 patients received hemodialysis at the participating centers. The cardiovascular-related deaths or hospitalizations for myocardial infarction, ischemic stroke, or congestive heart failure occurred in 21.4% of the 8000 patients who received cold dialysate and 22.4% of the 7413 patients in the standard temperature dialysate group, a statistically insignificant difference. More patients in the cold dialysate group reported feeling uncomfortably cold, with approximately one-quarter rating it as the worst possible feeling.

"A lack of cardiovascular benefit compounded by the likelihood of patient discomfort provides no justification to adopt cooler dialysate as a center-wide policy," said Amit Garg, MD, PhD, professor in the Division of Nephrology at Western University and scientist at the Lawson Health Research Institute, both in Ontario, during his presentation. "If I do prescribe cooler dialysate for certain patients, such as those with refractory interdialytic hypotension, I plan to do so more carefully and monitor how well it's tolerated."

During the question-and-answer session, Maarten Taal, MBChB, MMed, MD, professor of medicine at the University of Nottingham in the United Kingdom, noted the study might be the largest to date in patients undergoing dialysis. However, Taal questioned why the team chose 36.5°C when many dialysis units and most previous clinical trials of cold dialysate used 37°C as the standard temperature. Garg said that 36.5°C is standard in Ontario.

"The separation between our two groups is perhaps smaller than other trials," Garg said, and although he did not refute the results of previous trials that suggested a benefit of cold dialysate, he cautioned that 26 previous trials included 460 patients.

"We have to be quite cautious about our confidence in the previous results," Garg added.

Targeting IgA nephropathy

There is a desperate need for new therapies to reduce glomerular inflammation and kidney fibrosis in patients with IgA nephropathy, said Jonathan Barratt, PhD, the Mayer Professor of Renal Medicine at the University of Leicester in the United Kingdom. Currently, the standard of care is goal-directed, supportive therapy, but he said that many patients still experience glomerular inflammation and progressive kidney function decline.

Barratt presented the results of a phase 2 study (7) of an investigational therapy called cemdisiran. The drug is an RNA interference therapy that suppresses the production of complement component 5 in the liver. Barratt explained that complement activation is linked with glomerular inflammation and loss of kidney function.

He and colleagues randomized 31 patients with IgA nephropathy at high risk of kidney disease progression despite supportive care in a 2:1 ratio to receive 600 mg of cemdisiran subcutaneously or a placebo once every 4 weeks in addition to standard care. Patients in the cemdisiran group had a 37.4% adjusted geometric mean reduction in a 24-hour urine protein-to-creatinine ratio compared with the placebo group, suggesting reduced kidney damage. The cemdisiran group also had an average reduction of 98.7% in serum levels of complement component 5 between the start of the trial and week 32. The researchers will continue to follow the patients for a 156-week open-label extension.

"This novel RNA interfering therapy cemdisiran is capable of reducing the production of C5 in the liver," Barratt said. So far, he noted, that is translating into reductions of hematuria and proteinuria, but he cautioned that larger and longer studies are necessary.

Additional trials

Other high-impact trials presented at Kidney Week 2022 found the following:

- The hydrochloric acid binder veverimer did not slow CKD progression or improve physical function in patients with metabolic acidosis in the phase 3 VALOR-CKD trial (8), which enrolled 1480 patients at 191 sites in 34 countries (abstract FR-OR65, 2022).
- In the 6609-patient EMPA-KIDNEY trial, 10 mg of the sodium glucose co-transporter 2 (SGLT2) inhibitor empagliflozin daily reduced kidney disease progression or cardiovascular death in patients with kidney diseases, with or without diabetes, by 28% compared with placebo (abstract FR-OR68, 2022) (9).
- A meta-analysis of data from 13 SGLT2 inhibitor clinical trials found a 40% reduction in kidney disease progression and approximately one-quarter reduction in AKI with similar benefits for patients with CKD, with and without diabetes. Patients with diabetes did have approximately one event of ketoacidosis or lower-limb amputation per 1000 patient-years compared with none in the non-diabetic group, but presenter Natalie Staplin, associate professor and senior statistician in the Renal Studies Group at the University of Oxford, United Kingdom, concluded that the absolute benefits outweighed the risks (abstract FR-OR69, 2022) (10).
- A phase 2 study that randomized 140 patients with type 2 diabetes and CKD to isuzinaxib or placebo for 12 weeks found an average 21% reduction in the UACR in the intervention group versus a 2.5% UACR reduction in the placebo group. A larger benefit was seen in patients with very low kidney function (abstract FR-OR62, 2022) (11). ■

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ASN President's Update

The Kidney Revolution

Turning a Moment into a Movement

By Susan E. Quaggin

During this year's Kidney Week, I began my ASN President's address with a paradox: Nephrology, as we once knew it, is dying… and that is the best possible news!

In the 1960s and early 1970s, nephrologists might have had the heart-wrenching task of informing patients with kidney failure that they had not been selected to receive lifesaving dialysis—decisions made by panels, dubbed God committees. Former ASN President William M. Bennett, MD, FASN, recalls having to give this news to a young mother who developed acute kidney failure following labor and delivery (1).

And twenty-nine years ago, as a community, we celebrated the publication of the captopril trial that demonstrated benefits of angiotensin-converting enzyme inhibition to slow progression of diabetic kidney disease (2). However, this win for patients was followed by more than 2 decades of largely negative trials in our field, without a single new class of therapies identified to reduce the increased risk of mortality in patients living with kidney diseases.

In 1989, the Berlin wall came down, the worldwide web launched, and the Nobel Prize in Physiology or Medicine was awarded for the discovery of retroviral oncogenes. That same year, I attended my very first American Society of Nephrology Annual Meeting and chose nephrology as my specialty. I have seen the incredible transformation in our specialty, measured in these few short decades.

Today, we can stand up as a community and shout from the rooftops that nephrology's moment has most certainly arrived. Stagnation and lack of innovation do not define our field.

What marks this seismic shift?

- Perhaps it began in 2015, with the publication of the EMPA-REG trial (3), rapidly followed by a multitude of positive clinical trials with such powerful beneficial effects that we now have the capability to truly impact the progression of kidney diseases, reduce mortality, and treat comorbid conditions, including heart failure.
- Multiple, new therapeutic classes have been identified, including flozins, non-steroidal mineralocorticoid receptor antagonists, and glucagon-like peptide 1 agonists. In 2022 alone, the US Food & Drug Administration has granted nine full approvals and eight breakthrough designations for kidney-related treatments and devices, including new platforms to diagnose kidney diseases, treatments approved for lupus nephritis, gene-directed therapies, and innovations in dialysis.
- Breakthroughs in artificial intelligence, nanomedicine, stem cells, gene therapy, genetic discoveries, and beyond continue to emerge from laboratories throughout the world.
- We have witnessed major policy wins in the United States with the introduction of the federal policy to advance American kidney health in 2019 (4), the passages of immunosuppressive legislation in 2021 (5, 6), and bipartisan support for the Living Donor Protection Act of 2021 this year (7).
- Xenotransplantation has matured with the first in-human clinical trials set to begin as early as next year (8, 9)!

Concurrent with innovations and discoveries transforming our field, accelerants have brought us together as a global community like never before.

- Faced with natural and manmade disasters, we worked together to ensure our patients received the best possible care—whether during the pandemic or in war-torn regions, such as Ukraine. We combatted water issues in Jackson, MS, and the aftermath of hurricanes to care for our patients. We continued to fight even when exhausted and even in the face of personal loss.
- As civil unrest erupted around the globe, it placed a much-needed focus on disparities that drive diseases, including kidney diseases. Again, our community responded. We heard the calls to remove race from clinical algorithms. We were not the only specialty called upon, but we were the first and only specialty to date to provide a race-free formula (10). The kidney community led so others may follow.

Never—in my entire time in our field—has there been a time of such hope than at this moment, giving us the opportunity *and the charge* to turn this moment into a full-blown movement.

Every movement must have a vision. In 2019, ASN recrafted its vision statement to: A World without Kidney Diseases.

This is bold and ambitious. To some, it might seem impossible, but in the words of Evan Wolfson, a gay rights activist: "Ambitious goals are often seen as impossible until they are achieved, at which point they become inevitable, a matter of simple common sense and justice. **The movement is what happens in between**." If we are going to harness the promise of these powerful, new treatments and bend the arc of kidney diseases, we must push boundaries, and we must transmit innovations to all those who will benefit.

But first, it is essential that we know **who** has kidney diseases.

In the United States and in many countries, there are no standalone recommendations to screen for kidney diseases. This year, ASN worked with the National Kidney Foundation and other patient organizations to push the US Preventive Services Task Force to revisit its very outdated recommendation that there is no evidence to screen for kidney diseases because there are no interventions available other than managing diabetes and high blood pressure. With all the recent successes in our field, this statement is no longer true.

We must move kidney diseases out from the shadow of other diseases.

- It is unacceptable that 90% of the more than 37 million people in the United States living with kidney diseases do not know they are at risk for kidney failure (11).
- It is unacceptable that many patients "crash" into dialysis in the hospital setting without ever knowing their kidneys were at risk.

We must embrace prevention if we are to provide the best care, educate the public about the risks, and expand the living donor pool. In the words of former International Society of Nephrology President Adeera Levin, MD, "It is time to change the narrative and move from screening for kidney diseases to screening for kidney health."

We must stay vigilant, as new threats to our core values—patients first, always—emerge. In today's world, our diligence includes challenging policies, lawmakers, and misinformation that threaten our patients and our responsibility to provide the best care.

When we joined the profession of medicine, each of us recited an oath based on the Hippocratic Oath. As stated in the World Medical Association Declaration of Geneva, "I will not permit…any other factor to intervene between my duty and my patient" (12). We must stand up to policies that criminalize best care or threaten the interaction among physicians, health care team members, and our patients.

We must expand our advocacy and demand the increased funding necessary to combat the scope and reach of kidney diseases. In 2021, the National Institutes of Health spent an estimated $960 per patient with cancer, $560 per patient with Alzheimer's disease, and **only $18 per patient with kidney diseases** (13).

Why is one-third of dialysis treatment chairs in the United States filled with patients who are African American/Black, when only one out of eight people in this country is African American/Black? Why is 7% of the entire Medicare budget spent on treating kidney failure, and the powerful, new therapies that could delay the need for dialysis by an estimated *15 years* are not yet widely available to all (14)?

Could it be that those in charge—policymakers, executives, and purse-string holders—are not able to put themselves into the shoes of people or their families living with kidney diseases?

We know that when those in charge see—truly see—amazing things happen.

- October 30, 2022, marked the 50th anniversary of the Medicare End-Stage Renal Disease Program, a federal initiative ensuring dialysis was a right of all US citizens, which has saved an estimated 1 million lives (15). Historical records tell us that a patient and a nephrology fellow showed members of Congress what dialysis entailed. The patient, Shep Glazer, a salesman and father from New York, asked members of Congress, "If your kidneys failed tomorrow, wouldn't you want the opportunity to live?" (16).

We must make kidney disease personal. It is up to each of us to partner with patients, to listen to them, and to amplify their voices, which are by far the most powerful and the most influential.

We must also push for increased diversity of representation and decision-making power of those in charge and at every level of our community.

The kidney community has long recognized the need for diversity and is home to many trailblazers in this arena. Since 1989, ASN membership has diversified to include members from more than 130 countries. In 2013, ASN launched a diversity work group that became the Diversity, Equity, and Inclusion Committee in 2017 and the Health Care Justice Committee in 2021. This year, ASN welcomed the first five recipients of the ASN Loan Mitigation Pilot Program (for fellowship applicants from communities traditionally underrepresented in medicine) (17). These superstars will undoubtedly change our field.

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The Kidney Revolution

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While we must celebrate these advances, we must also recognize this is just the beginning. There is much more work to do. We must remain accountable each and every day and take action when we, or others, fall short. We will not achieve our shared goal—our ambitious vision—unless we continue to build diversity and transparency in decision-making and representation at every level of our field and wherever we have influence.

And when we succeed, where will this moment—this movement—take us? Twenty or 30 years from now, *Kidney News* will be reporting new genetic discoveries and other fundamental advances guiding prevention, treatments, and cures for every form of kidney diseases. Everyone will know their kidney "number," and we will be armed with powerful, new therapies and best treatments that will be available to all patients as we continue to shift the focus from kidney diseases to kidney health.

Nephrology, as I once knew it, has moved to a much brighter future, and I have never been filled with more hope or optimism for what we will accomplish together.

Undoubtedly, there will be challenges along the way. However, we do not shy away from challenges. To paraphrase Nelson Mandela: "The greatest glory in living lies not in never falling, but in rising every time we fall."

And remember, as physicians, health care team members, investigators, patients, and advocates, we always rise, and we always rise together.

- We stood up and said no to the status quo.
- We put an end to the God committees and death panels.
- We learned from the negative trials and persevered.
- We stood up to eliminate disparities and worked for true health justice.
- We fought against a devastating disease and stood up to those who did not care or who considered dialysis the endgame.
- We made the discoveries that have changed our field.

As I pen my last column as ASN President, I ask each of you to rise up in this moment and join the movement—the revolution.

It is up to us to make a world without kidney diseases not impossible but **inevitable**. ■

Susan E. Quaggin, MD, FASN, is with the Division of Nephrology and Hypertension, Northwestern University Feinberg School of Medicine, Chicago, IL, and is ASN President.

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Endothelin Antagonist Improves Control of Resistant Hypertension

Aprocitentan, a novel, dual endothelin A and B receptor antagonist, shows safety and efficacy in lowering blood pressure (BP) in patients with resistant hypertension, concludes a randomized trial in *The Lancet* (1).

The Parallel-group, Phase 3 Study with Aprocitentan in Subjects with Resistant Hypertension (PRECISION) trial enrolled 730 patients with resistant hypertension, drawn from 193 centers in 22 countries. Eligible patients had a sitting systolic BP of 140 mm Hg or higher, despite standardized background therapy with three anti-hypertensive medications, including a diuretic.

In the first part of the study, patients were assigned to 4 weeks of double-blind treatment with placebo or aprocitentan at a dose of 12.5 mg or 25 mg. This was followed by a single-blind phase in which all patients received aprocitentan at a dose of 25 mg for 32 weeks. In a subsequent withdrawal phase, patients were re-randomized to 12 weeks of double-blind treatment with aprocitentan at a dose of 25 mg or placebo.

After the first 4 weeks, the least-squares mean change in office systolic BP (primary outcome) was –15.3 mm Hg with the lower dose of aprocitentan and –15.2 mm Hg with the higher dose compared with –11.5 mm Hg in the placebo group. Differences in sitting BP were –3.8 mm Hg and –3.7 mm Hg with aprocitentan versus placebo; differences in 24-hour ambulatory systolic BP were –4.2 mm Hg and –5.9 mm Hg, respectively. The urine albumin-to-creatinine ratio decreased by –28% with aprocitentan at a dose of 12.5 mg and –31% with a 25-mg dose compared with a 5% increase with placebo.

In the withdrawal phase, office systolic BP increased by 5.8 mm Hg in the placebo group. Mild to moderate edema or fluid retention occurred in 9% of the lower-dose and 18% of the higher-dose aprocitentan group—leading to treatment discontinuation in seven patients—compared with 2% of the placebo group. Of 11 treatment-emergent deaths during the study, none was classified as treatment related.

Patients with resistant hypertension are at increased risk of cardiovascular events. Although the endothelin pathway is believed to play a role in the pathogenesis of hypertension, it is not targeted by current therapeutic options.

The dual endothelin antagonist aprocitentan offers an effective and well-tolerated, new alternative for resistant hypertension, the PRECISION findings suggest. The researchers believe this treatment has the potential to lower the risk of cardiovascular events in patients with resistant hypertension and associated comorbidity, such as diabetes, chronic kidney disease, albuminuria, and previous cardiovascular events. ■

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Ethical Challenges in Nephrology Addressed at Kidney Week 2022

By Karen Blum

Watching the slow decline and death of a single mother with kidney disease who was an undocumented immigrant, only able to access dialysis emergently once a week per state policy, spurred physicians at the University of Colorado School of Medicine to conduct research that helped change policies at their local hospital and then at the state level to increase access to dialysis care for undocumented immigrants.

The inspiring tale was one of four presentations on ethical challenges in nephrology at Kidney Week 2022 and the focus of the Christopher R. Blagg, MD, Endowed Lectureship in Kidney Diseases and Public Policy, entitled Dialysis for Patients in the Undocumented Immigrant Community in the United States.

There are approximately 11 million undocumented immigrants in the United States, about 70% of whom lack access to health care coverage, said Lillia Cervantes, MD, director of immigrant health and an associate professor in the Department of Medicine at the University of Colorado Anschutz Medical Campus in Denver. Approximately 6000 undocumented immigrants in the United States experience kidney failure, and access to kidney replacement therapy for this community varies throughout the country.

After the death of their patient, named Hilda, Cervantes and colleagues were motivated to see changes in state coverage for the 78 other undocumented immigrants receiving emergency dialysis at their hospital every 7 days, as well as others throughout the state. To support their case, they began by conducting qualitative interviews of 20 immigrants, asking about their experiences receiving emergency dialysis (1). The team found that patients experienced significant psychosocial distress, having to wait for symptoms to build, sometimes eating high-potassium foods to meet admission criteria. Many patients had near-death experiences and had been resuscitated.

The team also conducted interviews with 50 clinicians in Colorado and Texas, asking about their experiences providing emergency dialysis (2). The physicians described emotional exhaustion from witnessing suffering and high mortality. Some reported feeling they were jeopardizing patient trust by having to turn them away or described how they gamed the system, overexaggerating patients' symptoms to get them care. Others reported physical exhaustion from trying to bridge care or numb themselves from feeling too much empathy and moral distress because they were treating patients based on immigration status, not medical factors.

Cervantes and colleagues also studied mortality differences between those receiving emergency dialysis and those receiving standard dialysis (3). They compared 211 patients, of whom 169 received emergency dialysis in Colorado and Texas, and 42 received standard dialysis in San Francisco. After adjustments, the mean 5-year relative hazard for mortality among patients receiving emergency dialysis was 14-fold greater.

Additionally, they looked at health outcomes and costs associated with end stage kidney disease in this population, pulling data from a Texas study (4) that compared patients who transitioned to scheduled dialysis—because of a grant mechanism that provided subsidies for private health insurance—with those who continued receiving emergency dialysis. Patients who transitioned to scheduled dialysis had six fewer emergency department visits per month and 10 fewer hospital days per 6 months, with a net savings of approximately $6000 per person. An internal cost analysis of 78 patients found the diagnosis-related group for severe life-threatening hyperkalemia was approximately $6000 per weekly admission or $24,000 per person per month vs. Medicaid reimbursement for standard hemodialysis of $705 per week or $2820 per person per month—an eightfold difference. Based on these data, the hospital's chief financial officer agreed that accommodating the patient population was more important than the financial incentive, Cervantes said.

The team presented their data to the Colorado Emergency Medicaid program, and in February 2019, the program expanded to include kidney failure as a qualifying condition to receive emergency Medicaid, covering standard, three-times-per-week dialysis care. A study evaluating approximately 30 patients before and 5 months after they transitioned to standard dialysis (5) found that although some patients had moderate anxiety about navigating the changes in care, they experienced relief in receiving consistent care. Investigators noted improvements in all five quality-of-life subscales, using the Kidney Disease Quality of Life Instrument Short Form 36 (KDQOL SF-36), as well as in seven symptoms using the Edmonton Symptom Assessment System.

The work has continued, Cervantes said. She coauthored a paper (6) describing the steps that each state can take to change access to dialysis care and worked with the National Kidney Foundation to write a letter to state Medicaid directors in support of expanded access to kidney replacement therapy, including living donor transplant. ASN was a co-signer. She also is working on a manuscript demonstrating the nearly $13 million in cost savings for the state following the expansion of emergency Medicaid for the University of Colorado's 78 patients who are undocumented immigrants.

This year, the team gained access to home dialysis for the undocumented immigrant population and continues to push for additional legislation. New state bills provide subsidies to allow 10,000 undocumented immigrants to purchase private health insurance off the exchange and created the first state Medicaid program for undocumented immigrants under age 18, as well as for postpartum mothers.

"As clinicians, we're not traditionally trained to engage in advocacy or health policy change," Cervantes said. "We can each leave this world a better place like Dr. Blagg if through grit and perseverance we work toward health justice."

Shared decision-making

Another Kidney Week presentation, entitled Ethics of Shared Decision Making in Kidney Diseases, discussed the benefits and necessities of shared decision-making in advanced kidney diseases, a process now considered the gold standard for communication. In shared decision-making, clinicians and patients come together and try, through give and take, to optimize the patient's involvement in his or her care, said nephrologist Sara Davison, MD, a professor of medicine and bioethicist at the University of Alberta, Canada, and director of the university's Kidney Supportive Care Research Group.

The essential elements to this interchange (7) are that there are two parties involved and that they reach a decision by consensus. It means that one party cannot merely acquiesce, reluctantly agreeing to or passively accepting that decision, she said. Shared decision-making should be viewed as a collaboration in all aspects of clinical care, Davison said, and requires information, facts, values, and preferences from both the patient and clinician. "Only when both are actively considered and incorporated into decisions can they be actively shared," she said.

The process should begin at the earliest point of the clinical encounter, she said, and the clinician and patient should share in what is being investigated, including determining what is the health problem, what matters most to patients and would be considered an adequate solution, what patients want to achieve, and what they are willing to do. Then, when focusing on designing health-outcome goals, keep them specific, actionable, reliable, achievable, and realistic.

Davison advised, when formulating an action plan with patients, consider the following factors:

- **Connecting:** Who are the most important people in a patient's life? How often can they see them?
- **Enjoying life:** What activities or hobbies make them happy? What do they find so important that they cannot imagine living without?
- **Managing health:** How important is symptom control? How do they feel about quality versus quantity of life?
- **Functioning:** How are they doing with self-care and independence? How do they feel about asking for help?

Then, when having a conversation about moving forward, make sure to ask if it is acceptable to talk about a patient's options, ask if the patient would like to hear what you consider the most reasonable medical options, assess if the patient agrees to any of the options, confirm that your understanding about the patient's choice is correct, and then plan for the next step, Davison said. ■

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Letter to the Editor

Thank you for the special section, The Kidney Care Team, in the September issue of *Kidney News*, highlighting the collaborations among physicians, physician assistants (PAs), advanced practice registered nurses (APRNs), and pharmacists. The special section included numerous well-written articles that focused on the education, training, and responsibilities of the PA, APRN, and pharmacist team members, highlighting data that showed optimization of care for the nephrology patient through a team concept.

However, the article, "Use of Non-Physician Providers in the Nephrology Workforce Needs Careful Consideration and Urgent Attention," by Christin Giordano McAuliffe, lacked evidence-based data and gave conflicting recommendations regarding the role of the advanced practice provider (APP). The author noted the included figure and table were her opinion; however, the suggested utilization of APPs neither reflects current practice nor the Centers for Medicare & Medicaid Services' standard billing allowances. Furthermore, the suggestion of "under direct supervision" is contrary to standard practice in any setting and counters most state and federal laws regarding APP practice.

The shortage of nephrologists is a driving force behind the increased utilization of APPs within nephrology. These APPs are trained and educated in a manner that allows, and encourages, collaboration with board-certified nephrologists. Research demonstrates their inclusion increases access to care and provides high-quality care to the increasing number of patients with chronic kidney disease and end stage kidney disease (1–4). ■

Becky Ness, PA-C, MPAS, FNKF, is chair, National Kidney Foundation, Council of Advanced Practice Providers, and Peter Juergensen, PA-C, is president, American Academy of Nephrology PAs.

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Author's Response to Letter to the Editor

By Christin Giordano McAuliffe

I am grateful to Ms. Ness and Mr. Juergensen for their reply to my article, "Use of Non-Physician Providers in the Nephrology Workforce Needs Careful Consideration and Urgent Attention," published in this year's September edition of *Kidney News*. They raise the important issue of balancing financial interests with the ethical practice of medicine. The practice of ethical medicine and finance are two separate, often conflicting, domains of modern health care that may fail to overlap when incentives for sound clinical practice and ethical billing are misaligned with corporate goals of maximizing profit and seeking highest-level billing for each encounter.

To maximize profits, corporations are increasingly using non-physician providers with supervision models created by executives and scope-of-practice guidelines created through lobbying rather than clinical evidence. Physician assistants working in nephrology typically earn approximately half the salary of their physician colleagues and can bill 85% to 100% of physician fees, depending on state laws. Thus, there is a strong incentive for corporations to hire them. This cost savings is not extended to patients in the form of lower out-of-pocket costs. Rather, it is appreciated as profit into corporate coffers. "Legal" and "ethical" are a mismatch where quality of care is paramount. A *Cochrane Review* (1) found the studies presented by Ms. Ness and Mr. Juergensen woefully inadequate, and another, more recent study (2) found that physician-led care contributed to better patient outcomes and lower health care costs.

A fully trained physician assistant has significantly fewer training hours than a fully trained physician, and the content of that training is vastly different. As a former physician assistant myself, I appreciate this difference. I earned my medical degree and completed 5 years of postgraduate training to provide expert nephrology care. Properly supervised NPPs improve patient access and I invite all non-physician providers to join me in advocating for the highest quality and safest care for patients, rather than the interests of any health care professional or corporation. ■

Christin Giordano McAuliffe, MD, is a board-certified nephrologist in Nashville, TN, at Nephrology Associates, a practice that incorporates both nurse practitioners and physician assistants in the care of patients.

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Empagliflozin Improves Outcomes in CKD at Risk of Progression

Across a wide range of patients with chronic kidney disease (CKD), treatment with empagliflozin reduces the risks of progressive CKD and death from cardiovascular causes, according to a clinical trial report in *The New England Journal of Medicine* (1).

In The Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY), 6609 patients with CKD were randomly assigned to treatment with the sodium-glucose cotransporter-2 inhibitor empagliflozin at 10 mg/day or placebo. Eligible patients had an estimated glomerular filtration rate (eGFR) between 20 and 45 mL/min/1.73 m^2 or an eGFR between 45 and 90 mL/min/1.73 m^2 with a urinary albumin-to-creatinine ratio (UACR) of at least 200. Patients were "broadly representative" of patients with CKD with risk of disease progression. The mean age was 64 years, two-thirds were men, and 46% had diabetes.

At a median follow-up of 2 years, the groups were compared on a composite outcome of kidney disease progression, consisting of end stage kidney disease, sustained decrease in eGFR to less than 10 mL/min/1.73 m^2, sustained decrease in eGFR of at least 40% from baseline, and death from renal causes, as well as death from cardiovascular causes.

Rates of progressive kidney diseases or cardiovascular death were 13.1% in patients assigned to empagliflozin versus 16.9% with placebo. The benefit was consistent across eGFR ranges and in patients with or without diabetes. After an initial acute decrease, the empagliflozin group had a slower rate of decline in eGFR, with a difference of 0.75 mL/min/1.73 m^2 per year.

Empagliflozin was associated with a lower rate of all-cause hospitalization (hazard ratio, 0.86). Other secondary outcomes were similar between groups, including heart failure hospitalization, cardiovascular death, and all-cause mortality. Serious adverse events were similar between groups.

There are limited data on the benefits of empagliflozin for patients with CKD at risk of disease progression. The EMPA-KIDNEY results show that empagliflozin reduces CKD progression and cardiovascular death in a broad range of patients with CKD at risk for progressive disease. The researchers noted "consistent benefits" in patients with and without diabetes, those with an eGFR less than 30 mL/min/1.73 m^2, and those with UACR under 300. ■

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COVID-19 and the Future of Outpatient Dialysis

By Karen Blum

With infectious agents, such as monkeypox and *Candida auris*, emerging in the wake of peak pandemic, the Great Resignation, supply chain difficulties, and lingering sadness over the loss of patients or family members to COVID-19, it's no surprise that the health care and dialysis industries have had significant challenges, said Jeffrey Hymes, MD, executive vice president, global head of Clinical Scientific Affairs at Fresenius Medical Care North America. Hymes spoke during the Kidney Week 2022 Clinical Practice Session, A Look in the Crystal Ball: COVID-19 and the Future of Outpatient Dialysis. He offered some tips to stimulate a turnaround.

"We've had our own wave of early retirement, attraction of our staff to other careers that are less challenging, perhaps viewed as being less risky or demanding," said Hymes, who is also chief medical officer for care delivery at Fresenius.

Retaining employees is not only about money but also ensuring they feel safe, adequately trained, and well treated.

In his presentation, Dialysis Facility Staffing in the Wake of COVID-19, Hymes noted that new hires are experiencing less face-to-face mentoring from existing health care staff already stretched to its limits, and there is increased complexity in caring for dialysis patients. "The cliché is that people can go and flip burgers for about the same money that they can be a dialysis technician," he said.

In previous years, non-US-born nurses were a source of labor for dialysis centers, he continued. However, now, there are increasing requirements for these nurses to stay within their home countries, which are also experiencing turnover in health care. Nursing costs are rising as well, with some nurses being recruited out of dialysis centers to agencies for "hourly rates that are really unsustainable," Hymes said, sometimes reaching rates similar to reimbursement for dialysis treatment. Having a traditional nurse and an agency nurse working side by side for unequal pay can "drive dissatisfaction, disaffection, and resignation," he said.

Together, these elements can result in patients feeling forced to choose conservative care if being treated by staff who are less experienced and are under less supervision, Hymes said, which could increase the potential for adverse events. Additionally, he said, "It's so valuable for a patient who's on insulin or hemodialysis to get educated by a nurse about transplant and home dialysis. How can they do that when they're running as fast as they can bound up in PPE [personal protective equipment]?" Meanwhile, dialysis providers are seeing delayed or reduced admissions, resulting in financial losses.

There are four possible avenues that could help mitigate these risks, he said.

1. **Trends in end stage kidney disease (ESKD).** For the first time in years, the number of incident ESKD patients has fallen, according to the 2021 *US Renal Data System Annual Data Report* (1). This could be reflective of increased mortality among late-stage 4/early-stage 5 patients, as well as the inability of patients with chronic kidney disease (CKD) to have had appropriate referrals during the worst of the pandemic, Hymes said. It is possible that a focus on home therapies and transplantation will somewhat ease the burden in the clinics, he said. However, this requires that nurses and physicians have additional skills and are competent in training in peritoneal dialysis and home dialysis and in caring for patients following post-acute care stays in transplant centers. Furthermore, assigning the healthiest patients to home dialysis means that those in the clinics will be sicker.
2. **Therapeutic choices.** Home dialysis offers an opportunity to stretch nurses and nursing hours, said Hymes. Studies have shown that involving patients in shared care or self-care can reduce the burden on nurses (2). There also is excitement in the field about the impact of sodium glucose co-transporter 2 inhibitors, aldosterone antagonists, glucagon-like peptide 1 agonists, and other agents that can have a favorable effect on cardiovascular health and slow the progression of ESKD, potentially resulting in fewer patients with kidney diseases or healthier patients in the future.
3. **Staff training and deployment.** Retaining employees is not only about money but also ensuring they feel safe, adequately trained, and well treated by supervisors, Hymes said. Lengthening training and mentorship periods and limiting the number of patients for whom a new staff member oversees care can have positive effects, he said. Personality profiling is important to identify a good fit, as is having a career path that offers staff opportunities to advance. Virtual training can be used to allow staff to learn to handle complications, such as severe hemorrhage or cardiac arrest.

   Another example of employment satisfaction is expanding the scope of practice and allowing patient-care technicians and licensed practical nurses to practice at the top of their licenses. This could look like a few patient-care technicians serving patients on a 1:1 basis, with a nurse rounding to check on them and being available as needed, or providing supervision via video monitoring.
4. **Technology.** There are several technologies that also could help, Hymes said. These include programs to optimize schedules that ensure robust nurse and patient-care technician staffing when the clinic is most busy and less staffing when it is not. Centralized "control tower" programs can allow patient-care technicians to keep an eye on several patients at once from one location, for example, viewing computer monitors tracking vital signs. Technologies in development may allow for better blood volume monitoring, which could improve safety and reduce nursing time.

Additionally, continuous monitoring of blood pressure, pulse, and other vital signs used in other specialties has "huge potential" for dialysis centers, Hymes said, including monitoring of disease progression. Furthermore, ultrasound, artificial intelligence, and robotic programs can be used to guide needle placement, potentially increasing patient satisfaction and reducing damage to arteriovenous fistulas. ■

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mRNA-Based Therapeutics Poised to Provide Growing Therapeutic Options

By Bridget M. Kuehn

The day the first genetic sequence was posted for the SARS-CoV-2 virus on a public web server in China, Melissa Moore, PhD, and her colleagues at Moderna immediately got to work trying to develop an mRNA-based vaccine against the virus. Moore, the chief scientific officer emeritus at the company, described the experience and advances in mRNA therapeutics during a State-of-the-Art Lecture, entitled mRNA as Medicine, at Kidney Week 2022.

The team had already been working with National Institutes of Health scientists to develop mRNA vaccines. Over the next 2 days, together, they selected to target the virus' spike protein. A former graduate student of Moore's working at Moderna designed the mRNA sequence used in Moderna's COVID-19 vaccine in 1 hour. Within 45 days of the SARS-CoV-2 protein's sequence becoming available, the team had a vaccine available for a phase 1 clinical trial. Making the vaccine took approximately 2 weeks, Moore said. Waiting for quality control assays took most of the time.

"That's how good we've gotten by putting in all the work that we've done up until now and just how quickly we can make a new medicine," she declared.

Panel moderator Catherine Godson, PhD, who co-chaired the 2022 Kidney Week Committee, credited Moore's work with allowing the meeting to be held again in person. Moore noted in her talk that decades of basic research laid the groundwork that enabled the rapid deployment of mRNA vaccines and the growth of mRNA therapeutics.

"Dr. Moore's achievements and contributions are an absolute testament to the impact of basic research," Godson said. "She's asked big, important questions and applied ingenuity and meticulous attention to detail in pursuing the fundamental truths of nature."

DIY medicines

Moore described how mRNA therapies are the last development in the evolution of therapeutics. She explained that proteins have long been the target of small-molecule medicines. Now, they are used as biological treatments as well. "While [protein therapeutics] are incredibly useful, they do have their limitations," she said.

She noted that companies use mammalian cells in massive bioreactors dedicated to a particular therapeutic to produce protein biologics. Each therapeutic is unique and must undergo a battery of pharmacokinetic, pharmacodynamic, and toxicology studies. The proteins may also have slight variations from the protein produced in the human body.

Moore explained that protein biologics are primarily limited to proteins that act in the blood or interstitial fluids, but more than 90% of human proteins are made inside cells and cannot be used as protein biologics. "[Protein biologics] have been transformative in many ways," she said. "The problem is that biologics are limited to a small fraction of human proteins."

Molecular biologists first discovered mRNA in 1961 (1, 2), Moore said. She explained that DNA encoding a protein is copied into mRNA, which then serves as a blueprint for building the protein. She noted that cells are "chock full of messenger RNA" and the proteins they produce. "Messenger RNA is an essential component of all living organisms," she continued.

Moore said mRNA therapeutics have all three properties of classic medicines: a limited duration of effect, dose-dependent effects, and protein production dependent on the amount of mRNA administered. "The very simple idea of mRNA medicines is that instead of giving the patient a pre-made protein, we could simply provide them with instructions and the mRNA to make the proteins, and they become factories for their own medicines," Moore contended.

Running the gauntlet

It took decades of basic research on mRNA and the immune system, however, to recognize the therapeutic potential of mRNA, which can produce any protein inside a cell. Researchers quickly discovered a significant hurdle: Trying to deliver mRNA into cells triggered a major interferon response, Moore explained. "Over evolutionary time, we've developed very strong mechanisms to protect us from infection by RNA viruses," she said.

In 2004, scientists discovered Toll-like receptors that recognize single-stranded or double-stranded RNA entering cells (3). Other receptors recognize double-stranded RNA in the cytoplasm of the cell. Both trigger a robust innate immune response, Moore said. "If we are going to deliver messenger RNA, it's going to have to run the gauntlet of these innate immune sentinels," she commented.

Scientists discovered that the sentinels recognize uracil, one of the bases that make up RNA strands and distinguish them from DNA. However, a seminal 2005 paper showed how to get around this hurdle (4). Moore explained that the human body makes chemical modifications to uracil and other bases, and the study led by Katalin Karikó, Drew Weissman, and their colleagues at the University of Pennsylvania found that some chemical modifications to uracil could thwart the sentinels. Moore said that Moderna now uses a modified uracil called N^1-methylpseudouridine to make its mRNA medications. She explained that the modifications on N^1-methylpseudouridine prevent the receptors from getting into the correct confirmation to trigger the immune response.

Another challenge was getting mRNA through the body to the target, which sees mRNA as food, consuming it, Moore said. To do this and get the mRNA into cells, Moderna uses lipid nanoparticles, she noted.

Growing potential

With those hurdles now overcome, Moderna has created a streamlined process for manufacturing mRNA medicines. "Once you've found a delivery system that can get mRNA to the cell types of interest, you can easily make a new medicine simply by switching out the sequence of the mRNA," Moore said.

Moderna uses a computer algorithm that can generate mRNA sequences for proteins. Then, the company sends that information to its factory to make a DNA template and produce the mRNA. She said that the bioreactors needed to produce the mRNA are much smaller than those used to make protein medications. One facility can make many different medicines and pivot from one to another quickly.

Moderna has developed a portfolio (5) of investigational mRNA therapeutics, including several in clinical trials or entering the clinical trial phase. These include therapeutic vaccines for cancer that help the immune system recognize and destroy tumors. The company has also developed inhalable drugs for cystic fibrosis and heart disease therapies. No kidney disease therapies are in the pipeline yet, Moore said, but she is very excited about mRNA therapies for rare diseases. For example, all but 1 of 10 patients with propionic acidemia in a phase 1 trial receiving mRNA therapy for 1 year have been able to avoid emergency department visits for metabolic decompensation (6).

"We are very encouraged that mRNA not only has been demonstrated to be an incredibly efficacious platform for making vaccines but also for [making medicines] to treat chronic disease," she said.

She added that Moderna is very interested in pursuing treatments for diseases with no existing therapies. The company also encourages academics to work with it through its mRNA Access program (7). Moore said that the company has grown from approximately 827 people when the pandemic hit to more than 5000 today. Moore thanked all her colleagues for their hard work.

"We've been at this a long time," she concluded. "It was so gratifying to be in the right place at the right time with the right technology when the COVID-19 pandemic hit, and it has been a remarkable place to work for the last 5 years." ■

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The NephroWorldCup Takes Sport and Science to the Next Level

By Xavier Vela Parada and Tejas Desai

The second installment of The NephroWorldCup launched at Kidney Week 2022 last month. Re-engineered from the 2018 inaugural tournament, The NephroWorldCup adds more fun and excitement to an improved learning experience. This year's tournament taps into the global knowledge of cardiovascular, renal, and metabolic (CVRM) disease medicine. Like the FIFA World Cup, The NephroWorldCup is a quadrennial learning event where CVRM science from 32 nations (teams) compete on study design, clinical applicability and patient impact. Each team is given its own scouting report in which 1) the science is succinctly summarized, 2) videos from global experts are available for added perspective, and 3) contributions from nephrology, cardiology, and metabolic disease social media communities are provided (https://sites.google.com/view/nephroworldcup/scouting-reports/group-b/usa).

CVRM enthusiasts (e.g., providers, patients, advocates, and caregivers) select winning teams in a format identical to the FIFA World Cup. The NephroWorldCup walks each player through the four tournament phases—group, quarter-finals, semi-finals, and championship—so players of all experience levels can successfully navigate the tournament.

Players earn points based on the concordance of their selections against the pool of players. The more players in the tournament, the more competitive the game. That competition is summarized in the players' dashboard (https://sites.google.com/view/nephroworldcup/dashboard). The dashboard updates player performances and predictions in real-time, giving all players the competitive intelligence they need to earn maximum points.

Generous prizes await those who win (https://sites.google.com/view/nephroworldcup/prizes). ASN, the European Renal Association, and The European Society for Organ Transplantation are offering a combined 15 years of complimentary memberships to the top 12-point earners.

Anyone with a passion for CVRM science can play The NephroWorldCup. Individual and team entries are welcome. Hybrid (e.g., patient-provider and faculty-fellow) and cross-functional (e.g., cardiology-nephrology and hospitalist-endocrinology) teams are encouraged.

The NephroWorldCup: For the Love of Science and Sport. Game on and good luck!

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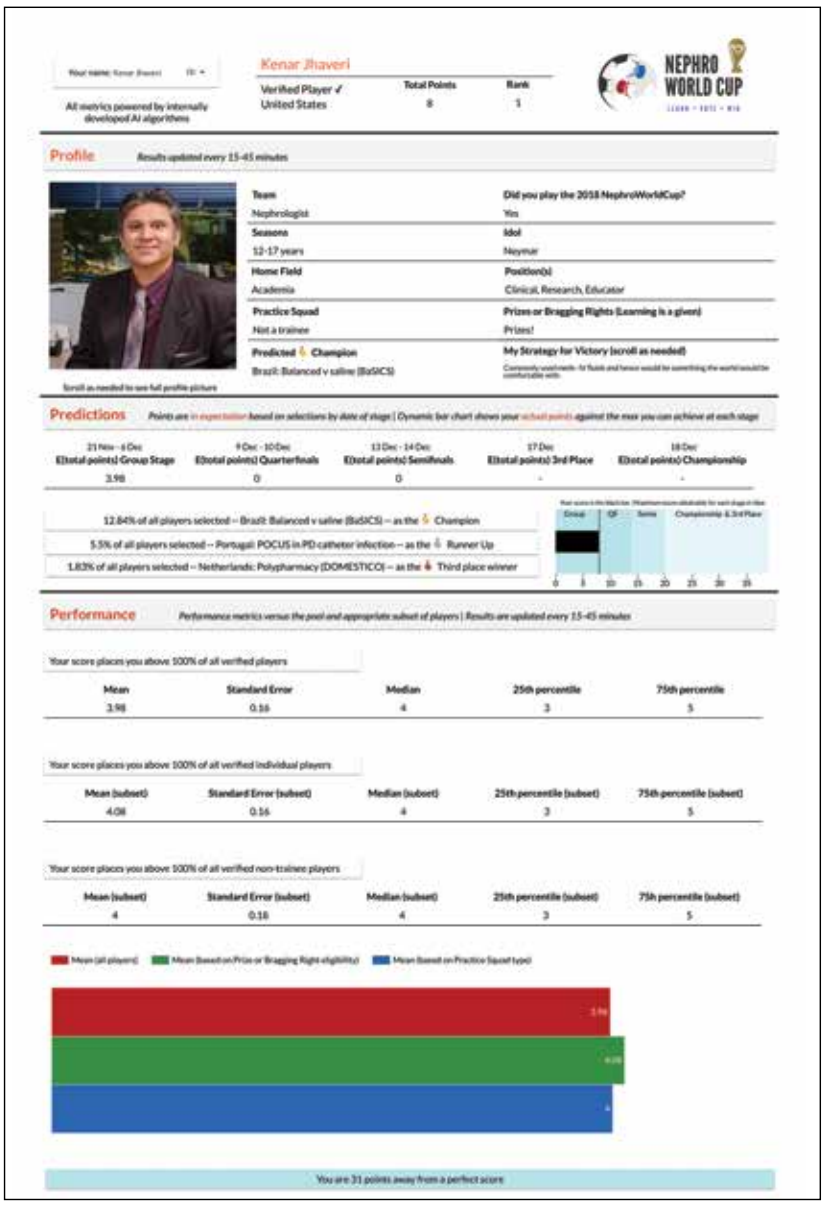
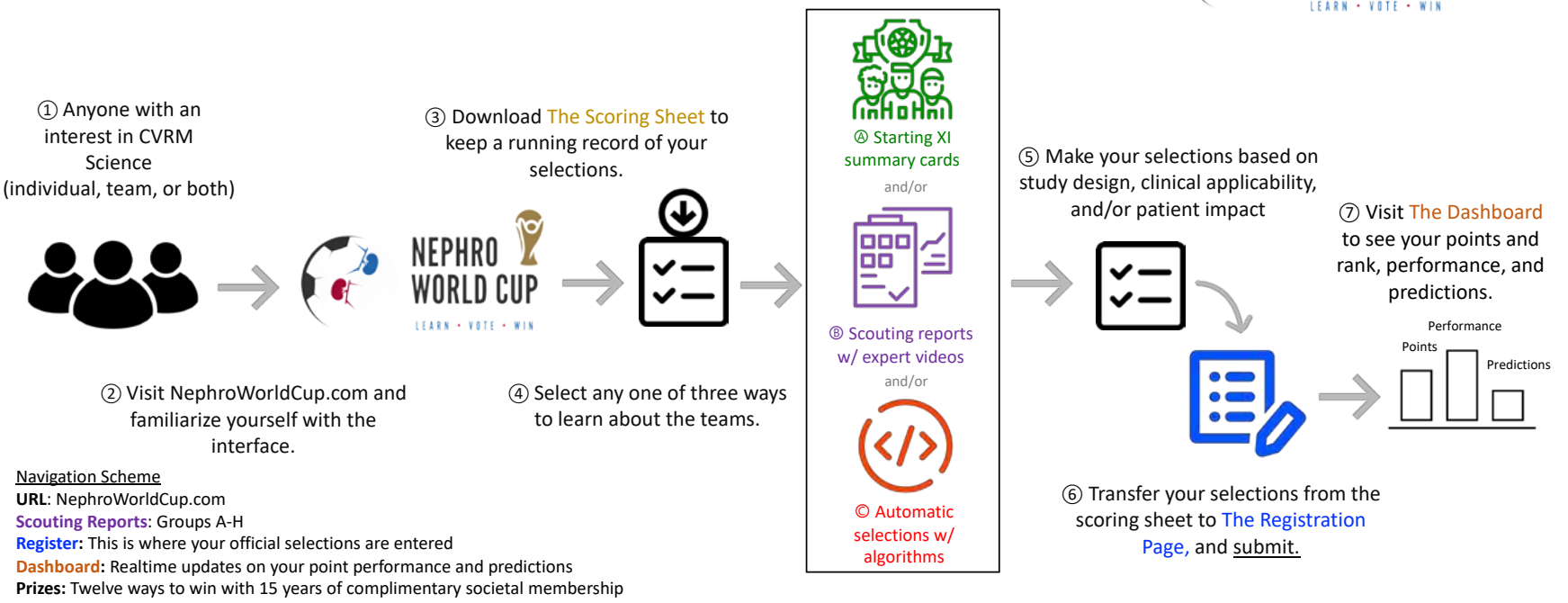
The authors report no conflicts of interest.



The 2022 NephroWorldCup.com Tournament: How to Play



Navigation Scheme
URL: NephroWorldCup.com
Scouting Reports: Groups A-H
Register: This is where your official selections are entered
Dashboard: Realtime updates on your point performance and predictions
Prizes: Twelve ways to win with 15 years of complimentary societal membership
Tips & Tricks: Scoring sheet | Starting XI | Strategy | Random selections
Match Results: Results of The Tournament will be posted here based on your votes
Rules: How to play | Sports(wo)manship | FAQs | Terms and conditions
Extras: In the literature | More CVRM to learn | Players forum | Wordle | #WeStandWithUkraine | Previous (2018) NephroWorldCup

Detective Nephron

Detective Nephron, world-renowned for expert analytic skills, trains budding physician-detectives on 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 57-year-old with a serum bicarbonate of 44 mmol/L.

Nephron (*excited*) Whoa! Finally...electrolytes stuff and possibly alkalemia.

Mac Trust me, you are going to enjoy this one!

Nephron Did you know that I get bored with low bicarbonate levels? High bicarbonate levels give me a rush, as the diagnosis is usually more interesting.

Mac Hmm...I can totally relate to that.

Pause

Mac She is in her 50s with a history of an unexplained rheumatologic disorder. The preliminary diagnosis is possible CREST syndrome. Her chief complaint is pain in her fingers and toes, worsening over the last few months. Two weeks ago, she had a black fingertip. Her blood pressure is 155/80 mm Hg and no edema on exam. Her fingers are cool to touch. She was given anticoagulation and calcium channel blockers. Blood cultures were negative.

Nephron Stop! Where is the electrolyte disorder? This is all good but....

Mac (*laughing out loud*) Since her admission, her serum bicarbonate levels have been in the 40- to 44-mmol/L range.

Nephron (*angry*) Oh, come on! And they noticed it on day 4? Why do we draw labs daily then?

Mac (*surprised*) I thought you love esoteric stuff. Well, they hydrated with normal saline for 2 days, and it did not change; stuck at 44. The ball's in your court now!

Nephron (*bored, rolling his eyes*) Metabolic alkalosis, a disorder that elevates the serum bicarbonate, can be seen with several disorders. Metabolic alkalosis consists of a generation phase and a maintenance phase. The generation phase refers to the initial event that causes the alkalosis. Metabolic alkalosis is generated either when hydrogen is lost or less commonly, when bicarbonate is gained. Once metabolic alkalosis occurs, the kidneys should be able to quickly correct it by excreting bicarbonate. However, there are factors that are present that do not allow the kidneys to do so; factors that "maintain" the alkalosis. We call this the maintenance phase. The main factors that maintain the alkalosis are low glomerular filtration rate, hypokalemia, hyperaldosteronism, and hypochloremia. In the past, hypovolemia was considered a factor—the so-called "contraction alkalosis"—but we know that experimentally, you can correct metabolic alkalosis by giving chloride without correcting the volume deficit. On the other side, you can correct the volume deficit without giving chloride, and the metabolic alkalosis persists. The issue is that we often lose fluids in the form of sodium chloride, so chloride is lost along with volume. When you give normal saline, you give volume, but you also give chloride. The proper term should be chloride-deficient metabolic alkalosis. Looks like they ruled it out. What is the serum creatinine?

Mac (*yawning*) Glad you asked. It has been in the 0.6- to 0.8-mg/dL range. She has normal kidney function, and hence, she should be able to excrete excess bicarbonate in the urine. She is not taking in any excess alkali (outpatient or inpatient). This alkalosis can only persist if there are maintenance factors.

Nephron (*winking*) Glad you are thinking what the kidney is thinking! So, if you think about generation phase, think in four buckets of how we can lose hydrogen: cellular shift, gastrointestinal (GI) losses, kidney losses, or less commonly, how we gain bicarbonate…usually due to external sources of bicarbonate.

Mac Her serum potassium level is 4.1 mmol/L and has been stable the last few days. No repletion was required. Yes, I know you will ask why hypokalemia causes metabolic alkalosis. To answer briefly, hypokalemia increases kidney ammoniagenesis and ammonium excretion, which can both generate and help to maintain the metabolic alkalosis. In addition, the loss of potassium will cause potassium to move from the intracellular space to the extracellular fluid. To maintain electroneutrality, the hydrogen ions will move inside the cells, which will lead to an increase in plasma bicarbonate levels.

Nephron (*laughing*) Well done, Mac. What about the GI losses?

Mac No vomiting; hydrogen loss can result from the loss of gastric secretions, such as vomiting, or less likely, from diarrhea in some patients. She had neither.

Nephron But wait! Why? Why? Why? Diarrhea? I thought that was causing normal anion gap metabolic acidosis.

Mac (*trying to remember*) Oh yes; you are correct. Diarrheal stool typically has a relatively high alkali concentration, and as a result, large-volume diarrhea typically generates metabolic acidosis but with rare disorders that increase GI chloride loss, such as congenital chloridorrhea, and in some patients with villous adenomas.

Nephron (*jumping in*) Oh...you are good!

Nephron (*to himself*) I actually do not miss Henle anymore. Wonder what he is up to these days.

Mac (*surprised*) Obviously! And by the way, normal calcium, ruling out calcium-alkali syndrome.

Silence

Mac Here are the rest of the lab data that may be helpful: normal white cell count, hemoglobin of 11.3 g/dL, and normal platelets. Serum sodium is 136 mmol/L, chloride is 105 mmol/L, and blood urea nitrogen is 7 mg/dL. As I mentioned earlier, serum total CO_2 is 44 mmol/L.

Nephron (*shocked*) Ah! I have a diagnosis for you already! But first, we need to make sure there is no hypertension or primary hyperaldosteronism here.

Mac (*jumping in*) Any cause of primary and inappropriate hypersecretion of mineralocorticoids can lead to and maintain a metabolic alkalosis, which is generally accompanied by hypertension and hypokalemia, but she has no such findings. Her hypertension has been stable for years, and her potassium has never been low in the past. In addition, her bicarbonate levels in the last few visits to her doctor were normal but started rising more recently. She is also not on any diuretics that can do this. Metabolic alkalosis and hypokalemia are characteristic features of Bartter and Gitelman syndromes. These disorders are produced by genetic defects in ion transporters but doubt she has that suddenly at the age of 57. She is also hypertensive.

Nephron So let's get back with our case. This is a nice discussion so far.

Mac (*confidently*) FYI…her urine studies done initially showed urine sodium of 40 mmol/L and Cl of 49 mmol/L. Her urine chloride was not low. In addition, we got some additional labs, such as lipids; serum complements were all normal. Her anti-nuclear antibody and rheumatoid factor were elevated.

Nephron Hmmm…. Did you notice that her serum anion gap is negative? Because of the patient's benign clinical appearance and a negative serum anion gap, the possibility of a spurious result should be entertained, my friend.

Mac (*confused*) Good point!

Nephron (*interrupting*) Not just a good point; it's an excellent point! We keep talking about low and high bicarbonate, but no one does a venous blood gas these days. Why not?

A few hours later

Mac We got a venous blood gas with a pH of 7.42, PCO_2 of 37, PO_2 of 157, and bicarbonate of 23. Interestingly, a serum chemistry done using i-STAT showed a total CO_2 of 24, and a routine lab test showed a serum bicarbonate of 39 mmol/L.

Nephron Is this serum bicarbonate real? With the history of unexplained rheumatic disease, digit pain, and elevated rheumatoid factor, please obtain immunoglobulin (Ig) levels and a serum free light chain assay.

A few weeks later

Mac (*nodding*) Her IgM level came back as 1700 mg/dL (very elevated), and a bone marrow done confirmed a diagnosis of Waldenstrom macroglobulinemia (WM). I assume the hyperbicarbonatemia was spurious, and we should ignore it?

Nephron (*puzzled*) Paraproteins may cause abnormal laboratory findings in three ways: 1) through the disease process itself, 2) by interacting with the target of an assay, and 3) by creating spurious results because of their interference with the assay method. Paraproteins have been shown to cause interference with the assays of multiple laboratory tests, including blood counts, sodium, calcium, phosphorus, lipids, coagulation profiles, iron studies, blood urea nitrogen, creatinine, bilirubin, C-reactive protein, glucose, uric acid, lactate dehydrogenase, and alkaline phosphatase. Among the paraproteins, IgM is more often the culprit because of its high molecular weight.

Mac Is it dependent on the load of the paraprotein?

Nephron I am not sure. Both false-positive and false-negative results may occur. In general, the paraprotein interference is concentration dependent. Some of the techniques many have used to avoid spurious results include alternate lab assay methods; doing i-STAT and venous blood gas levels, as you did; or removal of the paraprotein load before laboratory analysis. It is possible that the interference might be precipitation related to the IgM protein and the serum sitting in that milieu for a longer time compared with the emergent sample done.

Mac (*jumping in*) Bicarbonate is not that common. For some of the other electrolytes, this is a major concern. One can see pseudo hypercalcemia, pseudo hyperphosphatemia, and pseudo hypophosphatemia with paraproteinemia. It is critical to recognize these spurious electrolyte disorders to avoid unnecessary interventions that can potentially lead to harmful side effects.

Nephron Go get this patient some chemotherapy!

Mac (*confused*) Yes; apparently, she is on a bendamustine-based therapy already.

A few weeks later

Nephron (*to himself*) Tough case for Mac, but she did a great job.

Mac You know, you were on target! The patient's subsequent outpatient laboratory findings were that after she began treatment for WM with bendamustine and rituximab, her serum IgM levels returned to the normal range, and the routine chemistry results also revealed a bicarbonate level within the normal range.

Nephron (*jumping in*) There we go again. From a simple lab abnormality, you made a systemic diagnosis!

Mac (*surprised*) I agree with you, and it is prudent to have a high clinical suspicion of abnormal laboratory values in the setting of paraproteins, as the machines are usually unable to detect interference on their own. As a result, we could reduce or prevent incorrect diagnoses, prolonged hospital stays, prescriptions of inappropriate treatment, and morbidity or mortality in our patients.

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, and to Helbert Rondon, MD, associate professor of medicine, University of Pittsburg Medical Center, PA, for their editorial assistance. Please send correspondence regarding this section to: kjhaveri@northwell.edu or kdj200@gmail.com.

Wearables May Provide Early Kidney Health Warning Signs

By Bridget M. Kuehn

Over the past 15 years, John Rogers, SM, PhD, executive director of Northwestern University's Querrey Simpson Institute for Bioelectronics in Evanston, IL, has been working on translating modern electronics technology into wearable or implantable medical devices.

He is attempting to reformulate the hard, brittle, silicone components that have turned mobile devices into powerful pocket computers into flexible materials that clinicians could use on or in the human body. These devices can function as wearable "second skin" or lie on the surface of an organ, such as the brain, heart, or kidney, and capture clinical-grade measurements to drive research breakthroughs or clinical care innovation.

"We're aiming to drive progress at the boundaries [among] engineering, science, and medical science," said Rogers, who is also the Louis Simpson and Kimberly Querrey Professor of Materials Science and Engineering, Biomedical Engineering and Medicine at Northwestern's McCormick School of Engineering. "We are envisioning a future where electronics adopt physical properties that are compatible with soft tissues and living systems."

Devices developed by Rogers are already monitoring health data in thousands of people around the globe. Now, he is working on two projects that could change how nephrologists monitor kidney function in patients with kidney disease or identify signs of kidney transplant rejection, according to his State-of-the-Art presentation at Kidney Week 2022.

Global reach

Rogers and his team have developed electronics that mimic the skin's thickness and mechanical, thermal, and water-permeation properties. They have used this technology to create a portfolio of wireless devices useable almost anywhere on the body. The devices can be used individually or integrated to provide full-body health-status assessments in the hospital or at home.

"You can think of these devices almost like a second skin that can go on your natural skin in a way that is physically imperceptible to the patient…that allows for quantitative clinical-grade measurements," Rogers said.

Working with colleagues in the neonatal intensive care units and pediatric intensive care units at the Ann & Robert H. Lurie Children's Hospital of Chicago and Prentice Women's Hospital, Rogers developed and tested these devices to monitor vital signs in newborns (1). One sticker-like device on the chest measures electrocardiogram and temperatures and can help measure respiration and heart rate. A second device, wrapped around the foot, continuously measures blood oxygenation. When the two devices are synchronized, they can monitor blood pressure or blood flow.

"The two devices are monitoring all of the vital signs currently captured today with cumbersome, high-cost, wire-based biosensors," Rogers said. In 2021, a startup company, called Sibel Health, launched by Rogers and colleagues, received US Food & Drug Administration (FDA) clearance for the device (2).

In partnership with the Bill & Melinda Gates Foundation, Save the Children, Merck for Mothers, and the Steele Foundation for Hope, Rogers and his team deployed this technology to monitor the vital signs of more than 15,000 mothers and infants living in lower resource settings in Kenya, Ghana, Zambia, India, Pakistan, and Mexico (3). The battery-powered devices upload the data they collect to a privacy-protected Cloud-based platform where clinicians can remotely analyze them.

A collaboration between Rogers and neurosurgeons at Northwestern resulted in the creation of a device to measure cerebrospinal fluid flow in children who have a shunt to remove excess brain fluid buildup (4). The team designed the tool to help patients determine if their shunt is working. Patients with a shunt who experience nonspecific symptoms, such as a headache or nausea, which can indicate a life-threatening emergency, shunt failure, or a more benign condition, must rush to the emergency department for assessment. However, the new tool uses tiny heaters and temperature sensors in a skin-like device to measure the fluid flow. "It turned out to be very easy to do," Rogers said. "We could immediately see if there's flow or no flow."

Rogers said that the team launched another company, called Rhaeos, Inc., to develop the shunt-monitoring device (5) and is conducting clinical trials necessary to gain FDA clearance for the device.

Kidney applications

Rogers is also working with Lorenzo Gallon, MD, medical director of the Translational Medicine program and director of the Transplant Nephrology Fellowship at Northwestern, to create implantable sensors to detect the earliest signs of kidney transplant rejection. The goal is to be able to treat patients as early as possible and avoid the need for a biopsy.

"The hypothesis was that if you are undergoing a rejection, then the transplanted kidney would likely increase in temperature, and there might be an increase in blood flow associated with that rejection event," Rogers said.

They have created an implantable, wireless sensor that attaches to the kidney and measures blood flow and temperature. After testing the device in rats, they found that temperature—but not blood flow—provides an early warning about rejection. Now, they have begun testing the device in pigs. The new version of the device attaches to the kidney with a tiny barb, can also measure blood oxygenation, and uses a wirelessly recharged battery.

The skin-like sensors that Rogers and his team have created can also be used to measure compounds in sweat to assess hydration. The team is marketing the Gx sweat patch in stores through a partnership with Gatorade. Rogers created a version of the device for the National Kidney Foundation's 2017 "Heart Your Kidneys" promotional event at South by Southwest (6). The team has also created a color-changing sticker version of the device, which provides an easier, less cumbersome approach than existing wearables, that clinicians are using at Lurie Children's Hospital to measure sweat chloride levels to screen for cystic fibrosis.

They have since worked to develop a skin sensor that can measure creatinine, urea, and pH in sweat. The vision is to enable at-home kidney screening, but first, the team needs to understand how sweat creatinine levels correspond with those in urine or blood.

"That's a topic of ongoing research," Rogers said. He said he hoped his talk at Kidney Week would lead to feedback about the potential kidney applications he is developing and perhaps generate new collaborations.

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Championing Kidney Care in 2022

In 2021, ASN launched "We're United 4 Kidney Health," an initiative that repositions nephrology as a specialty committed to early detection and treatment, not just the "failure" and "end-stage" aspects of kidney treatment. We're United 4 Kidney Health presents a rallying cry that shows how the kidney community can advance the field by embracing four priorities:

1. **INTERVENE EARLIER** to prevent, diagnose, coordinate care, and educate.
2. **TRANSFORM TRANSPLANT** and increase access to donor kidneys.
3. **ACCELERATE INNOVATION** and expand patient choice.
4. **ACHIEVE EQUITY** and eliminate disparities.

ASN is committed to achieving a world without kidney diseases and has made strides to do so in 2022 by championing policies across these four priorities that will improve the lives of individuals living with kidney diseases.

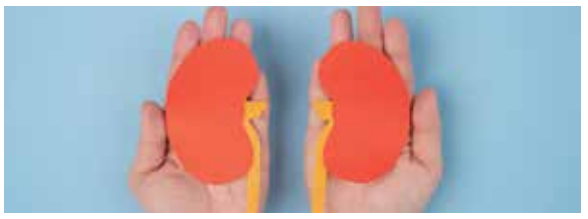
INTERVENE EARLIER to prevent, diagnose, coordinate care, and educate

It is crucial to prevent or slow the progression of kidney diseases and related comorbidities for the more than 37 million Americans living with kidney diseases.

This year, the US Preventive Services Task Force (USPSTF) accepted the nomination of chronic kidney disease screening for evaluation to potentially become a future recommendation for preventive services, as proposed by ASN, the Coalition for Kidney Health (C4KH), and other kidney health organizations. ASN advanced support for this recommendation for early kidney disease testing across the federal government and throughout Congress. If the USPSTF concurs with ASN and other advocates and recommends screening for kidney diseases, it will be a foundational step in enabling other federal policies that better support earlier detection and intervention.

With the expansion of Medicare Advantage (MA) in 2021 to allow people with kidney failure to enroll in MA, culminating in a 77% enrollment increase among people with kidney failure in the first year of allowed election, people with kidney failure have increased options for health care coverage. However, the proliferation of private health coverage raises concerns that existing data sets based on Medicare claims data, such as the US Renal Data System, will not completely capture the data of patients enrolled in MA plans, limiting the ability of researchers to understand and improve care for people with kidney failure. ASN advocated for Medicare and the National Institutes of Health to address this data gap in MA expansion and to include complete data of people with kidney failure.

In 2022, ASN made further progress supporting research of new biomarkers to diagnose kidney diseases and implement health equity improvements. Language was included in the fiscal year (FY) 2023 funding package requesting the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to prioritize research of new biomarkers and health equity interventions. In addition, ASN collaborated to increase funding for kidney disease awareness and surveillance and the Centers for Disease Control and Prevention. With new therapies available to patients that can slow the progression of kidney diseases, building public awareness about kidney diseases is an important step to aid in earlier intervention. Furthermore, the Center for Medicare and Medicaid Innovation made history by introducing the first-ever measure of health equity in the End-Stage Renal Disease (ESRD) Treatment Choices Model.



TRANSFORM TRANSPLANT and increase access to donor kidneys

The second priority of the We're United 4 Kidney Health campaign revolves around fundamentally improving the current transplant ecosystem, as 13 Americans die each day on a 100,000-person kidney transplant wait list.

Increasing transparency and accountability in the US transplant system has been a top priority for Congress and an area of significant interest for the Biden-Harris administration in 2022. ASN submitted testimony to the Senate Finance Committee calling for system reforms to increase transparency so that patients can be "provided the opportunity to be true partners in their care."

ASN also made extensive recommendations to the Centers for Medicare & Medicaid Services (CMS) and the Health Resources and Services Administration in response to requests for information, seeking perspectives on ways to improve transplant care that builds on the implementation of an earlier rule establishing objective and verifiable performance metrics for organ procurement organizations.

Culminating in years of advocacy on behalf of ASN and many other stakeholders, ASN also welcomed and supported proposals from CMS to provide dental coverage for people with kidney failure—a requirement for obtaining a kidney transplant that currently hinders some people's access to the optimal therapy. The society also greeted with great enthusiasm the plans of CMS to operationalize coverage of lifetime immunosuppressive drug coverage for kidney transplant patients, as mandated by Congress in 2019, the outcome of years of advocacy by ASN and many other key patient and health professional organizations.

Last year, ASN helped secure the re-introduction of the Living Donor Protection Act in Congress, and this year secured a historic number of co-sponsors (155 in the US House of Representatives and 43 in the Senate). This legislation will remove barriers to donation and increase access to life-saving transplants by ensuring that insurance companies offering life, disability, and long-term care plans do not deny or limit coverage or raise premiums based on an individual's status as a living organ donor. This bill was also the focus of Kidney Community Advocacy Day, during which ASN brought together nearly 20 other organizations advocating for individuals with kidney diseases and health professionals to jointly urge Congress to enact these donor protections.

ACCELERATE INNOVATION and expand patient choice

The third priority centers on accelerating innovation and expanding the therapeutic options available to patients.

Advocacy by ASN and the rest of the kidney community secured $5 million in congressional appropriations for the Kidney Innovation Accelerator (KidneyX) and $2.204 billion for NIDDK in FY 2022 (October 1, 2021–September 30, 2022). NIDDK received a funding-level increase over FY 2021 funding levels of approximately 3.4%.

Finally, ASN also worked regulatory avenues to advance reimbursement for increased innovation in transitional add-on payment adjustment for new and innovative equipment and supplies and transitional drug add-on payment adjustment, while developing payment pathways for an artificial kidney and other innovations and addressing barriers and quality measurement in home dialysis.

ACHIEVE EQUITY and eliminate disparities

The entire kidney community must begin to address a number of disparities affecting individuals with kidney diseases in an effort to achieve equity.

ASN supported the expansion of telehealth as a result of the COVID-19 public health emergency (PHE), which serves as a valuable tool in eliminating disparities to achieve equity. The flexibilities and waivers, however, would expire after 151 days from the end of the COVID-19 PHE period. Virtual care and telehealth are now significant pieces of the US health care system, and ASN supports efforts to ensure the certainty of these services after the PHE. ASN has urged Congress to permanently extend pandemic telehealth flexibilities, including removing home and originating-site restrictions and establishing parity between audio and visual telehealth services. Congress is finalizing a 2-year extension of these telehealth policies while working toward a permanent extension.

ASN also supported the collection and use of social determinants of health and related data—such as zip codes—within the Medicare ESRD program. One particular approach is to identify areas of higher concentration of dual-eligible (both Medicare and Medicaid) individuals and higher uses of low-income subsidies. ASN is working with the US Department of Health and Human Services to identify and address inequities and disparities across overall health and kidney care. As noted, if the USPSTF issues recommendations to screen for kidney diseases, for which ASN, the C4KH, and other kidney health organizations are advocating, it would significantly advance the federal government's ability to support earlier diagnosis and intervention—elements of care that are crucial to ensuring equitable access to interventions that slow the progression of disease.

Individuals with kidney diseases around the world are uniquely vulnerable to the effects of climate change, which are expected to become more extreme and occur with greater frequency. More broadly, the population of people with kidney diseases is disproportionately composed of people at a socioeconomic disadvantage who are also bearing the greatest burden of climate change. Recognizing that climate change threatens to increase the incidence and prevalence of kidney diseases, disrupt access to care, and widen inequity in kidney health, ASN released a statement on climate change and supports polices and interventions to address climate change.

ASN championed kidney care across the federal government and throughout Congress in 2022 to help further kidney health policies. These advances build further momentum as the nephrology community unites toward a world without kidney diseases. Updates about these policies will be provided in subsequent issues of *Kidney News* and in real-time via @ASNAdvocacy on Twitter.

Findings

Ambulatory BP and "Dipping" Affect Prognosis in CKD

Even when ambulatory blood pressure (BP) is at goal, the absence of nocturnal dipping is associated with increased cardiovascular and kidney risks in patients with chronic kidney disease (CKD), reports a study in the *American Journal of Kidney Diseases*.

The prospective cohort study included 906 patients with stage 2 to stage 5 CKD seen at three Italian nephrology clinics. All had hypertension, defined as an office BP of 140/90 mm Hg or higher, or use of anti-hypertensive medications at any level of BP. The mean age was 64 years, and 61% of patients were men. Approximately 26% of patients had diabetes; the mean estimated glomerular filtration rate was 41 mL/min/1.73 m^2.

Patients were classified into four groups, based on systolic ambulatory BP levels at or above goal, defined as systolic BP (SBP) less than 135 and nocturnal SBP less than 120 mm Hg, and the presence or absence of nocturnal dipping, defined as a nighttime-to-daytime SBP cutoff of 0.9. Overall, 49.1% of patients had ambulatory BP above goal without nocturnal dipping, 11.8% had ambulatory BP above goal with nocturnal dipping, 20.5% had ambulatory BP at goal without nocturnal dipping, and 18.6% had ambulatory BP at goal with nocturnal dipping.

On multivariable analysis, patients with ambulatory BP above goal were at increased risk of cardiovascular events, both without dipping (hazard ratio [HR], 2.79) and with dipping (HR, 2.05). Analysis of kidney disease progression showed a similar pattern: HR, 2.40 and 2.11, respectively. Patients who had ambulatory BP at goal but without dipping were also at increased risk: HR of 2.06 for cardiovascular events and HR of 1.82 for kidney disease progression compared with patients at goal and with nocturnal dipping.

The study is one of the first to analyze the combined prognostic effects of ambulatory BP and nocturnal dipping among patients with CKD. The results show increased cardiovascular and kidney disease risk for patients with CKD with ambulatory BP above goal, regardless of nocturnal dipping status.

For patients with ambulatory BP at goal, the absence of nocturnal dipping is a risk factor for both adverse cardiovascular and renal outcomes. The investigators concluded: "Our results confirm the essential role of ambulatory BP measurement to define accurately the hypertensive burden and circadian BP profile, thus allowing better risk stratification in these high-risk patients" [Borrelli S, et al. Dipping status, ambulatory blood pressure control, cardiovascular disease, and kidney disease progression: A multicenter cohort study of CKD. *Am J Kidney Dis*, published online ahead of print June 13, 2022. doi: 10.1053/j.ajkd.2022.04.010; https://www.ajkd.org/article/S0272-6386(22)00709-0/fulltext].

Stopping RAS Inhibitors Does Not Alter eGFR Outcome in Advanced CKD

In patients with advanced chronic kidney disease (CKD), discontinuation of renin-angiotensin system (RAS) inhibitor therapy does not affect the long-term rate of decline in kidney function, according to a report in *The New England Journal of Medicine*.

The randomized, open-label STOP-ACEi trial included 411 patients with advanced, progressive CKD, with an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73 m^2. Patients were assigned to either continue or discontinue RAS inhibitor therapy. For those in the discontinuation group, any other type of guideline-recommended anti-hypertensive agent could be used; RAS inhibitors could be restarted only as a "last resort." Change in eGFR at 3 years was assessed, along with secondary outcomes.

The least-squares mean change in eGFR was not significantly different between groups: 12.6 mL/min/1.73 m^2 in patients who discontinued RAS inhibitors and 13.3 mL/min/1.73 m^2 in those who continued therapy. Three-year rates of end stage kidney disease or renal replacement therapy were similar as well: 62% and 56%, respectively. There was no significant difference in serious adverse cardiovascular, vascular, or heart failure events.

Patients in the discontinuation group initially had higher blood pressure values, but this was corrected over time. Other secondary outcomes were also similar, including a 6-minute walk test and protein level.

In patients with mild to moderate CKD, RAS inhibitors slow the decline in eGFR and progression to advanced kidney diseases. However, there is limited evidence showing any benefit of RAS inhibitors in patients with advanced CKD. One observational study reported increases in eGFR after RAS inhibitor discontinuation in this group of patients.

Within its limitations, the STOP-ACEi trial shows no clinically relevant change in eGFR and no increase in the rate of long-term eGFR decline, after stopping RAS inhibitor therapy in patients with advanced, progressive CKD. The findings "do not support the hypothesis that the discontinuation of RAS inhibitors in patients with advanced and progressive chronic kidney disease would improve kidney function, quality of life, or exercise capacity," the researchers concluded [Bhandari S, et al. Renin-angiotensin system inhibition in advanced chronic kidney disease. *N Engl J Med*, published online ahead of print November 3, 2022. doi: 10.1056/NEJMoa2210639; https://www.nejm.org/doi/10.1056/NEJMoa2210639].

Medicare Restricts Concurrent Hospice and Dialysis for Veterans

Among veterans with end stage kidney disease (ESKD), use of concurrent hospice care and dialysis is lower when Medicare is the hospice payer, compared with Veterans Health Administration (VA) coverage, reports a study in *JAMA Health Forum*.

The retrospective study included 70,577 VA-enrolled veterans who initiated dialysis and died between 2007 and 2016. Of these, 18,420 veterans received hospice care. Rates of concurrent dialysis and hospice care were compared across hospice payer groups: Medicare, VA-financed inpatient hospice, or VA-financed community-based hospice.

The hospice payer was Medicare for 89% of patients. Overall, 28% of veterans continued to receive dialysis after hospice enrollment. On adjusted analysis, rates of concurrent dialysis and hospice care were significantly higher for those with VA-financed hospice care: 57% with VA inpatient hospice and 41% with VA community hospice compared with 24% with Medicare.

Overall, 87% of dialysis treatments after hospice entry were paid by the VA, including patients on Medicare with hospice diagnoses other than ESKD. Veterans with concurrent hospice and dialysis care spent a median of 43 days in hospice compared with just 4 days for those who stopped dialysis after starting hospice.

Medicare's policy regarding hospice care requires patients to forfeit coverage for treatments related to their hospice diagnosis. In contrast, the VA has a more liberal policy, acknowledging the potential palliative benefits of some disease-directed therapies.

"Medicare hospice policy may substantially restrict access to concurrent hospice and dialysis care among veterans with ESKD," the researchers wrote. They discussed their findings in the context of ongoing programs exploring the feasibility of offering concurrent hospice and dialysis services under Medicare [Wachterman MW, et al. Association of hospice payer with concurrent receipt of hospice and dialysis among US veterans with end-stage kidney disease: A retrospective analysis of a national cohort. *JAMA Health Forum* 2022; 3:e223708. doi: 10.1001/jamahealthforum.2022.3708].

Social Determinants of Health Affect Transitions from CKD to Kidney Failure

Education, employment, and other social determinants of health (SDOH) are associated with increased odds of suboptimal transitions from advanced chronic kidney disease (CKD) to kidney failure, reports a study in *Nephrology Dialysis Transplantation*.

The retrospective analysis included 1070 patients with advanced CKD at a Canadian kidney disease clinic who progressed to dialysis or kidney transplantation between 2010 and 2021. The mean age was 63 years, and approximately two-thirds of the patients were male; the mean estimated glomerular filtration rate was 18 mL/min/1.73 m^2.

Levels of education, employment status, and marital status were assessed from routine patient data. These SDOH exposures were analyzed for association with suboptimal outcomes involving the transition from CKD to kidney failure: inpatient (as opposed to outpatient) dialysis starts, preemptive (as opposed to delayed) access creation, and preemptive kidney transplantation.

On multivariable analysis, all three SDOH exposures were associated with suboptimal progression to kidney failure. For patients with less than a high school education, the odds ratio (OR) for inpatient dialysis start was 1.71. Patients who were unemployed were more likely to have an inpatient dialysis start (OR, 1.85) and were less likely to have preemptive access creation or preemptive kidney transplantation (OR, 0.53 and 0.48, respectively). Patients who were unmarried were more likely to have an inpatient dialysis start (OR, 1.44) and were less likely to have preemptive access creation (OR, 0.67).

Even at specialized multidisciplinary clinics, many patients with advanced CKD have suboptimal transitions from advanced CKD, which are associated with increased morbidity and mortality. SDOH, defined as "non-medical factors that have a major influence on health outcomes," might affect the transition from CKD to kidney failure.

Patients with SDOH related to education, employment, and marital status are more likely to experience suboptimal outcomes related to the transition from advanced CKD to kidney failure, the new findings suggest. The researchers concluded, "As a nephrology community, we must identify 'upstream' targets to improve care for our CKD population if we hope to achieve more equitable outcomes for our patients" [Hundemer GL, et al. Social determinants of health and the transition from advanced chronic kidney disease to kidney failure. *Nephrol Dial Transpl*, published online ahead of print October 31, 2022. doi: 10.1093/ndt/gfac302; https://academic.oup.com/ndt/advance-article-abstract/doi/10.1093/ndt/gfac302/6783171?redirectedFrom=fulltext&login=false].

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A Journey into Clinical Evidence in the Treatment of Membranous Nephropathy

By Fernando Caravaca-Fontán, Gema Fernández-Juárez, and Manuel Praga

Among all glomerular diseases, membranous nephropathy is perhaps the one in which greater progress has been made during the last 5 years, both in the understanding of the pathogenesis and treatment. Myriad target antigens have been identified so far, which has led to the proposal of reclassification of membranous nephropathy based on the underlying pathogenesis (1). In addition, the latest results from clinical trials on membranous nephropathy have sparked renewed interest in the management of the disease (2).

Five landmark trials—Ramachandran et al. (3), GEMRITUX (4), MENTOR (5), and STARMEN (6), together with a fifth trial (RI-CYCLO) (7), which essentially was a pilot study (Figure 1, Table 1)—have been performed on membranous nephropathy. These results have had a significant impact on current patient management, some of them reflected in the latest Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (8).

In the trial by Ramachandran et al. (3), the authors compared the efficacy of tacrolimus corticosteroids with cyclical corticosteroids-cyclophosphamide at 6 and 12 months, showing comparable results, although with different adverse effect profiles (mainly higher incidence of nephrotoxicity in the calcineurin inhibitor arm).

The GEMRITUX trial (4) evaluated the effects of rituximab compared with non-immunosuppressive treatment. Interestingly, no significant differences were observed within the first 6 months, which corresponded to the primary endpoint. However, in the extended follow-up beyond 6 months, the remission rate was significantly greater in patients treated with rituximab.

The MENTOR trial (5) compared rituximab with cyclosporine, and although no significant differences were observed in the rate of complete/partial remissions at 12 months (60% vs. 52%), at 24 months, a significantly greater number of patients remained in remission in the rituximab arm, mostly due to a large number of relapses after the discontinuation of cyclosporine. Thus, rituximab was found to be non-inferior to cyclosporine for induction of remission at 12 months but statistically superior at 24 months in terms of maintenance of remission.

The STARMEN trial (6) compared a sequential regimen based on tacrolimus and rituximab, with cyclical corticosteroids-cyclophosphamide. The primary outcome (complete/partial remission at 24 months) occurred in 84% in the corticosteroids-cyclophosphamide group versus 58% in the tacrolimus-rituximab group, with the rate of complete remissions being significantly greater in the former group. Remarkably, the number of relapses was also lower in the group treated with corticosteroids-cyclophosphamide.

Finally, the RI-CYCLO trial (7) aimed to assess the effect of rituximab compared with a cyclical corticosteroids-cyclophosphamide scheme for the induction of remission. At 12 months, the number of patients with complete remission was lower in the rituximab arm compared with corticosteroids-cyclophosphamide (16% vs. 32%), whereas at 24 months, complete remission was similar (42% vs. 35%). Thus, the authors concluded that there was no superiority of rituximab versus the cyclical regimen, although a pragmatic comparison of these two regimens would require a global non-inferiority trial.

Based on some of these trials, the latest KDIGO guidelines suggest different therapeutic approaches according to risk stratification (2, 8). For patients at low risk, immunosuppressive therapy may not be required unless additional risk factors for disease progression are present. For patients at moderate risk, the guideline suggests a wait-and-see approach or immunosuppressive therapy based on rituximab or calcineurin inhibitor ± glucocorticoids. Conversely, for high-risk patients, rituximab, cyclophosphamide plus glucocorticoids, or calcineurin inhibitor plus rituximab are suggested.

Taken together, these trials represent a major step forward for evidence-based membranous nephropathy and will likely contribute to a more personalized treatment. Nevertheless, further research is needed to fill several knowledge gaps in both the diagnosis and treatment of several resistant forms of the disease. ■

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The authors report no conflicts of interest.

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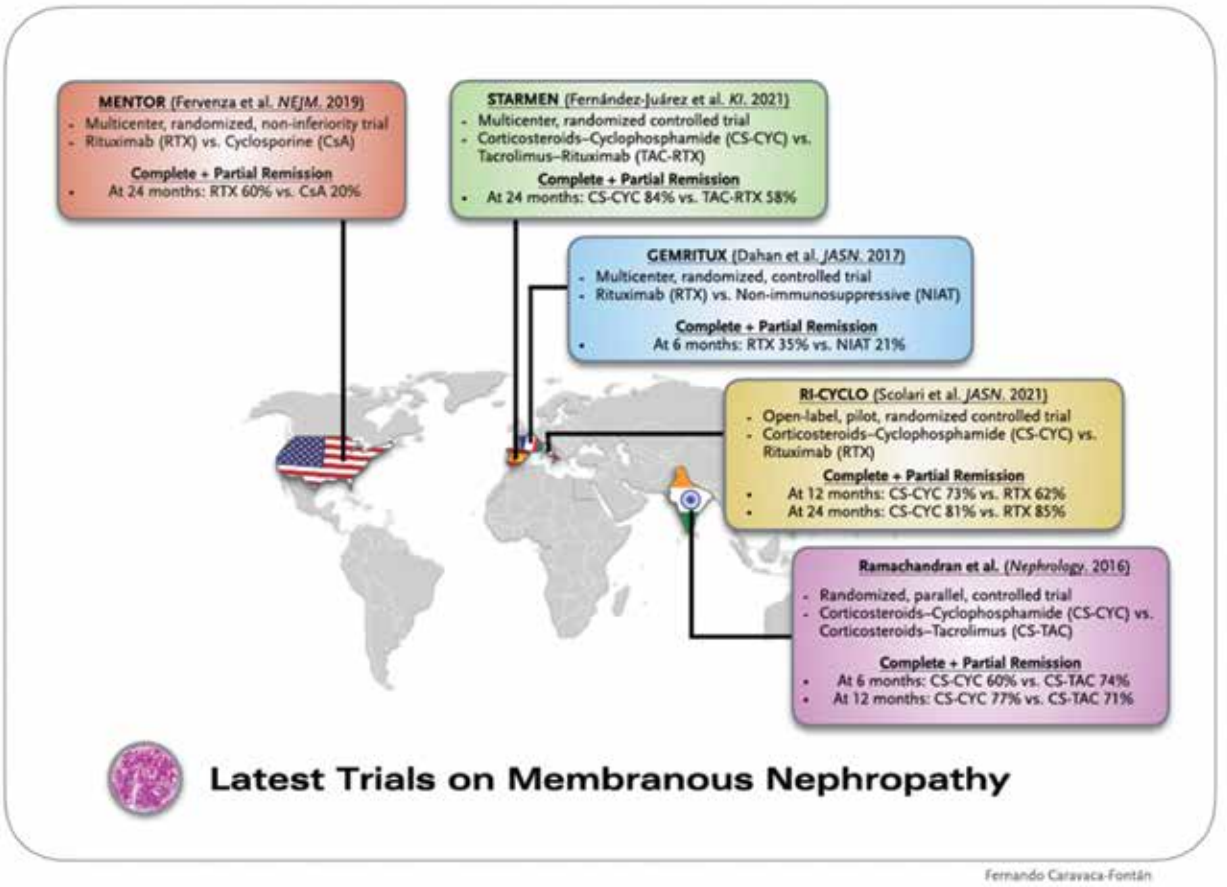
Figure 1



A Journey into Clinical Evidence in the Treatment of Membranous Nephropathy

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Table 1. Summary of recent trials on membranous nephropathy

Study		Ramachandran et al.	GEMRITUX	MENTOR	STARMEN	RI-CYCLO
Year		2016	2017	2019	2021	2021
Patients, No.		70	77	130	86	74
Country		India	France	North America	Spain and Netherlands	Italy and Switzerland
Design		Randomized, parallel group, controlled trial	Multicenter, open-label, randomized controlled trial	Multicenter, randomized, non-inferiority trial	Multicenter, prospective, randomized controlled trial with two-parallel design	Open-label, pilot, two-parallel arm, randomized controlled trial
Inclusion criteria		Adult patients with biopsy-proven MN	Adult patients with biopsy-proven MN	Adult patients with biopsy-proven MN	Adult patients with biopsy-proven MN	All patients with incident MN
Run-in phase, months		6	6	3	6	3
Intervention		CS-CYC group: MP at months 1, 3, and 5; CYC at months 2, 4, and 6 CS-TAC group: Oral TAC for 12 months and oral prednisone for 6 months	NIAT group RTX + NIAT group: 375 mg/m2 RTX on days 1 and 8; at the end of month 6, possibility to reinfuse RTX	RTX group: RTX 1 g on days 1 and 15; second course of RTX at 6 months if no CR CsA group: Oral CsA for 12 months and tapered after 2 months	CS-CYC group: MP at months 1, 3, and 5; CYC at months 2, 4, and 6 TAC-RTX group: Oral TAC for 6 months + RTX 1 g at month 6	CS-CYC group: MP at months 1, 3, and 5; CYC at months 2, 4, and 6 RTX group: RTX 1 g on days 1 and 15
Outcomes		Primary: CR or PR at 6 and 12 months Secondary: eGFR and adverse events	Primary: CR or PR at 6 months Secondary: proteinuria, albumin, creatinine, PLA2Rab	Primary: CR or PR at 24 months Secondary: CR/PR at months 6, 12, 18, and 24; time-to-treatment failure; ESKD	Primary: CR or PR at 24 months Secondary: CR/PR at months 3, 6, 12, 18, and 24; relapses; IR	Primary: CR at 12 months Secondary: CR/PR at months 6, 12, 18, and 24; proteinuria; SAE
PLA2Rab positivity, n/N (%)		48/70 (69)	55/75 (73)	96/130 (74)	53/69 (77)	41/62 (66)
Baseline proteinuria (g/day) or UPCR (mg/g), median (IQR)		CS-CYC group: 5.4 ± 2.7 CS-TAC group: 6.8 ± 3.6	NIAT group: 7195 mg/g (5363–8965) RTX + NIAT group: 7680 mg/g (4584–10,339)	RTX group: 8.9 (6.8–12.3) CsA group: 8.9 (6.7–12.9)	CS-CYC group: 7.4 (4.8–11.3) TAC-RTX group: 7.4 (6.7–11.6)	CS-CYC group: 6 (5–9) RTX group: 6 (4–10)
Results	**CR + PR, No. (%)**	At 6 and 12 months: CS-CYC group: 21 (60) and 27 (77) CS-TAC group: 26 (74) and 25 (71)	At 6 months: NIAT group: 8 (21) RTX + NIAT group: 13 (35)	At 24 months: RTX group: 39 (60) CsA group: 13 (20)	At 24 months: CS-CYC group: 36 (84) TAC-RTX group: 25 (58)	At 12 and 24 months: CS-CYC group: 27 (73) and 25 (81) RTX group: 23 (62) and 22 (85)
	CR, No. (%)	At 6 and 12 months: CS-CYC group: 13 (37) and 18 (51) CS-TAC group: 13 (37) and 19 (54)		At 24 months: RTX group: 23 (35) CsA group: 0 (0)	At 24 months: CS-CYC group: 26 (60) TAC-RTX group: 11 (26)	At 12 months: CS-CYC group: 12 (32) RTX group: 6 (16)
	IR, No. (%)	At 6 and 12 months: CS-CYC group: 29 (83) and 31 (88) CS-TAC group: 30 (86) and 28 (80)	At 6 months: NIAT group: 3 (12) RTX + NIAT group: 13 (50)	At 24 months: RTX group: 33 (66) CsA group: 6 (13)	At 3 and 6 months: CS-CYC group: 20 (77) and 24 (92) TAC-RTX group: 9 (45) and 14 (70)	At 12 months: CS-CYC group: N/P (56) RTX group: N/P (62)
	Relapses, No. (%)	None*		RTX group: 2 (5) CsA group: 18 (53)	CS-CYC group: 1 (2) TAC-RTX group: 3 (12	CS-CYC group: 6 (22) RTX group: 3 (13)
SAE, No. (%)		CS-CYC group: 24 (69) CS-TAC group: 29 (83)	NIAT group: 5 (13) RTX + NIAT group: 6 (16)	RTX group: 11 (17) CsA group: 20 (31)	CS-CYC group: 8 (19) TAC-RTX group: 6 (14)	CS-CYC group: 5 (14) RTX group: 7 (19)

CR, complete remission; CS, cyclical corticosteroid; CsA, cyclosporine; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease; IQR, interquartile range; IR, immunological response; MN, membranous nephropathy; MP: methylprednisolone; NIAT, non-immunosuppressive anti-proteinuric treatment; N/P, not provided; PLA2Rab, phospholipase A2 receptor antibodies; PR, partial remission; RTX, rituximab; SAE, serious adverse event; TAC, tacrolimus; UPCR, urinary protein-to-creatinine ratio.
*An extended follow-up study by the same group found a relapse rate of 40% and 6.7% in CS-TAC and CS-CYC groups at 24 months, respectively.

The Rapidly Changing Landscape of IgA Nephropathy Treatment

By Dana V. Rizk

Since the initial description of immunoglobulin A nephropathy (IgAN), significant advances have been made in our understanding of the disease pathogenesis (1). These advances have spurred exciting, new research targeting the various steps in this autoimmune process. But the relatively slow kidney function decline in most IgAN patients has made the implementation of clinical trials with hard outcomes (such as a 50% reduction in estimated glomerular filtration rate [eGFR], kidney failure, or death) quite challenging. In 2016, a partnership between ASN and the US Food and Drug Administration (FDA) identified proteinuria as a surrogate marker of disease progression and response to therapeutic interventions (2). Subsequently, the IgAN community witnessed a renewed interest from the pharmaceutical industry in the treatment of this rare disease and a proliferation of clinical trials (Figure 1). In 2021, the updated Kidney Disease: Improving Global Outcomes (KDIGO) guidelines prioritized clinical trial participation in the hierarchy of disease management strategies (3). Review of all ongoing trials is beyond the scope of this article; it is worth mentioning a few studies that have already yielded exciting results.

The TESTING trial reevaluated the benefit of systemic steroid treatment (4). Use of a lower dose of prednisolone along with antibiotic prophylaxis resulted in favorable kidney outcomes while mitigating serious adverse events.

The phase 3 NefIgArd trial tested the efficacy of localized steroids at the intestinal mucosal surface where the disease is thought to originate (5). The study showed a 27% relative reduction in proteinuria compared with placebo at 9 months, earning targeted-release budesonide conditional approval by the FDA and recently by the European Medicines Agency.

Another phase 3 trial, PROTECT (6), evaluated the efficacy of sparsentan (a combined angiotensin receptor blocker [irbesartan] and endothelin receptor antagonist) compared with irbesartan alone. The interim results favored sparsentan with a 49.8% mean reduction of proteinuria from baseline versus 15.1%. These positive outcomes are being considered by the FDA for conditional approval.

The DAPA-CKD trial included 270 patients with IgAN in whom dapagliflozin (sodium-glucose cotransporter 2 inhibitor [SGLT2]) reduced the primary end point of a ≥50% decline in eGFR, kidney failure, or kidney/cardiovascular death by 71% (7). The EMPA-KIDNEY study results recently published supported further the benefit of SGLT2 inhibitor use in patients with non-diabetic kidney disease including IgAN. (8)

Many other ongoing trials in earlier stages of clinical development are investigating the safety and tolerability of novel therapies targeting B cells (thought to be responsible for the production of the galactose-deficient IgA1 autoantigen and its autoantibody), as well as the alternative, lectin and terminal complement pathways (9). The rapidly changing treatment landscape in IgAN has energized the nephrology community. Experience gained from current studies will undoubtedly serve as a road map for treating other rare glomerular diseases. Therefore, IgAN patients and their providers have the unique opportunity but also a tremendous responsibility to engage and deliver timely and successful clinical trials. ■

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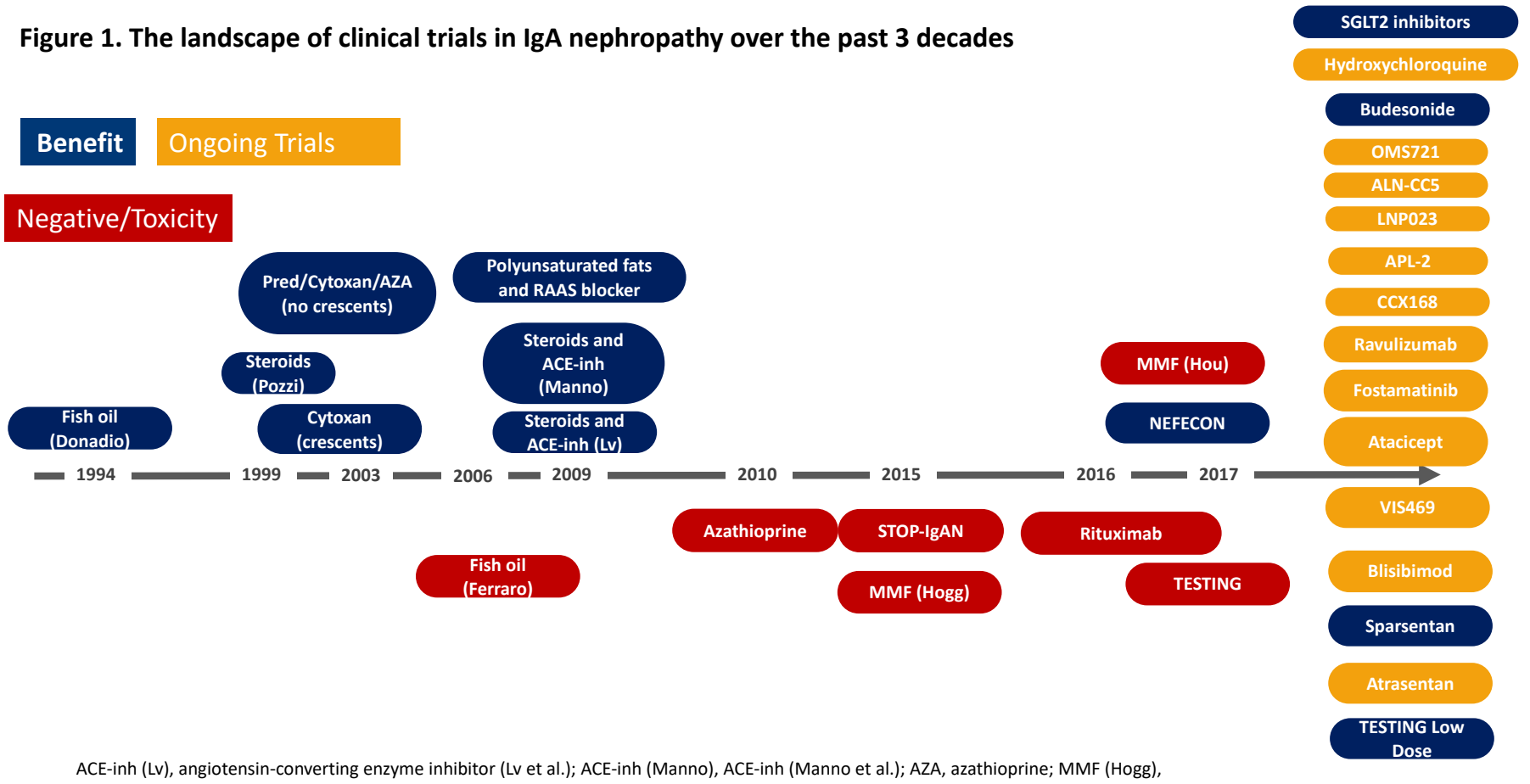
Figure 1. The landscape of clinical trials in IgA nephropathy over the past 3 decades



ACE-inh (Lv), angiotensin-converting enzyme inhibitor (Lv et al.); ACE-inh (Manno), ACE-inh (Manno et al.); AZA, azathioprine; MMF (Hogg), mycophenolate mofetil (Hogg et al.); MMF (Hou), MMF (Hou et al.); Pred, prednisone; RAAS, renin-angiotensin-aldosterone system; SGLT2, sodium glucose co-transporter 2.

Early versus Late Initiation of Dialysis in AKI

By Vineet Behera and P. Manu Dogra

Dialysis is the cornerstone of the management of kidney failure for acute kidney injury (AKI) and chronic kidney disease (CKD). However, dialysis is associated with complications, adverse events, cost, and decreased quality of life, especially if started too soon. Therefore, selecting the ideal time to initiate dialysis is paramount. Early initiation versus delayed initiation of dialysis has been a point of constant debate in nephrology. Earlier initiation of kidney replacement therapy (KRT) may help with fluid and electrolyte balance, removal of uremic toxins, and the prevention of uremic complications, but it exposes people to dialysis-related adverse events and greater time spent on dialysis.

The timing is generally well established for patients with progressive CKD who may be dialyzed with the onset of uremic symptoms or with the presence of uremic complications. The landmark Initiating Dialysis Early and Late (IDEAL) trial (1) showed that planned, early initiation of dialysis in CKD stage 5 was not associated with an improvement in survival or clinical outcomes compared with a delayed initiation.

Several randomized controlled trials (RCTs) have been performed over the past decade to attempt to answer the question of when dialysis should be initiated for patients with AKI. The ELAIN trial (2) was published in 2016 and examined almost entirely surgical patients (n = 231) from a single center. The study found a significant reduction in 90-day mortality with an early strategy compared with a delayed strategy. The AKIKI trial (3) was published just 1 week later but was a multicenter study that included patients in medical intensive care units (ICUs) who were more critically ill. AKIKI found no significant difference between early- and late-start strategies. The important drawbacks of these studies were that ELAIN was a single-center study that included only surgical patients and had a small sample size, and the AKIKI trial included only patients with advanced AKI, and only 50% of the patients received dialysis. The IDEAL-ICU (4) and STARRT-AKI (5) trials tried to correct the drawbacks of previous studies but found no significant difference in both strategies. The AKIKI 2 trial (6) tried to compare a delayed strategy with a more delayed strategy (both >72 hours) and also did not find any difference between the two approaches. In most studies, the early strategy was associated with fewer chances of AKI-related complications, such as hyperkalemia or pulmonary edema, and the delayed strategy was associated with less dialysis requirement and a higher incidence of spontaneous recovery of AKI.

A meta-analysis by Xiao et al. (7) included 12 RCTs with 5423 participants. The study found that early or delayed dialysis had similar rates of all-cause mortality at day 28 (38.7% vs. 38.9%). Another meta-analysis of 11 trials (8) showed no statistically significant effects on ICU length of stay, hospital length of stay, recovery of kidney function, and KRT dependence.

To date, most RCTs have not favored early or late initiation of dialysis but have robustly shown that early initiation has no benefit over late initiation of dialysis. The comparisons among the RCTs are challenging, due to variable causes of AKI, use of different populations, and use of different definitions for "early" and "late" dialysis. In conclusion, there is no optimal timing for KRT, and whether early dialysis is superior to delayed dialysis is a matter of controversy.

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The authors report no conflicts of interest.

Key RCTs: Early- vs late-initiation dialysis in AKI KidneyNews

	ELAIN	AKIKI	IDEAL-ICU	STARRT-AKI	AKIKI 2
Study setting	Germany, one center	France, multicenter	France, multicentric	Multicentric	France, multicentric
AKI eligibility	KDIGO stage 2 AKI + NGAL >150 ng/mL	KDIGO stage 3 AKI + on ventilator/pressors	RIFLE (failure) AKI early septic shock	KDIGO stage 2/3 + critically ill	KDIGO stage 3 AKI + oliguria >72 h, BUN >40
KRT–early/late	<8 h/8–12 h	<6 h/>72 h (or BUN >40/complications)	<12 h/>48 h	<12 h/>72 h or complications	Above/complications or BUN >50
Participants, No.	231	620	488	2927	278
% KRT (early vs late)	100% vs 91%	98% vs 51%	97% vs 62%	97% vs 62%	98% vs 79%
Mortality	90 day (39% vs 54%)	60 day (48% vs 50%)	90 day (58% vs 54%)	90 day (44% vs 44%)	60 day (44% vs 55%)
RCT favors	**Early KRT**	**No difference**	**No difference**	**No difference**	**No difference**
Other key results	**Favors early KRT** (time on KRT; kidney recovery; hospitalization duration)	**Favors delayed KRT** (fewer CRBSI; earlier diuresis post-AKI)	**Mixed results** Delayed (38% did not need KRT); early (fewer emergencies)	**Favors delayed KRT** (fewer adverse effects; KRT dependence)	**Mixed results** Delayed (fewer mortality 60 days); more delayed (fewer need KRT)
Features/ limitations	Mostly surgical patients; most early cases would have self-recovered	Advanced AKI patients; both IHD and CRRT used	Used RIFLE criteria; nonblinded; stopped early for futility	Heterogeneity in groups; KRT decision at physician discretion	Compares late vs very late (not early); BUN levels to start KRT
References	Zarbock et al. (2)	Gaudry et al. (3)	Barbar et al. (4)	Bagshaw et al. (5)	Gaudry et al. (6)

No difference in early vs late initiation of dialysis in AKI (early KRT – fewer AKI complications; delayed KRT – fewer need KRT) @BeheraVineet

BUN, blood urea nitrogen; CRBSI, catheter-related bloodstream infection; CRRT, continuous renal replacement therapy; IHD, intermittent hemodialysis; KDIGO, Kidney Disease, Improving Global Outcomes; NGAL, neutrophil gelatinase-associated lipocalin; RIFLE, risk, injury, failure, loss of kidney function, and end stage kidney disease.

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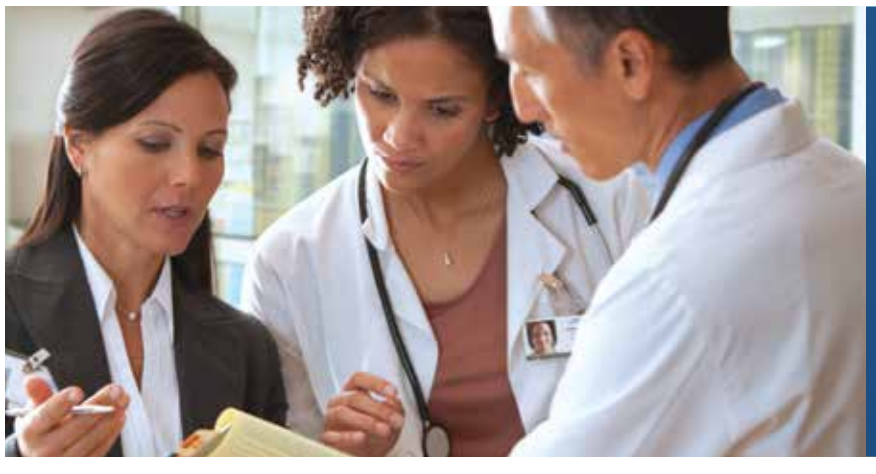

Balanced Salt Solutions: Are We Crystal Clear or Still Murky?

By Aniketh Prabhakar and Vinant Bhargava

Intravenous fluids are ubiquitously given to hospitalized patients, both critically and non-critically ill. The most widely used intravenous fluid remains 0.9% sodium chloride (normal saline). Although both balanced crystalloids and saline have been available for clinical use and scientific scrutiny for more than 100 years, only in recent years has normal saline been under the spotlight with several studies questioning whether this is the best solution to use.

Animal studies have shown unfavorable effects of normal saline by demonstrating that it causes acidosis because of a supranormal chloride concentration leading to detrimental vasodilation in the critically ill. This acidosis also leads to an increase in inflammation. In isolated dog kidneys and septic rats infused with saline, renal vasoconstriction was noticed, which was attributed to increased tubular chloride reabsorption. Furthermore, in healthy human volunteers, studies have demonstrated that intravenous normal saline administration leads to reduced kidney blood flow and decreased cortical tissue perfusion (1–3).

The alternative—i.e., balanced crystalloids (with a composition resembling plasma in both chloride and sodium concentrations)—may prevent the decrease in cortical perfusion and alleviate the increase in tubuloglomerular feedback because of their lower chloride content. So, what is the evidence?

Initial trials

Yunos et al. (4), in collaboration with Australian colleagues, published the Chloride High Level of Resuscitation Infusion Delivered Evaluation (CHLORIDE) trial, the first study, to our knowledge, demonstrating that balanced salt solutions might reduce incident acute kidney injury (AKI). This was a prospective, open-label study in which saline and balanced solutions (Hartmann's solution, Plasma-Lyte 148 and chloride-poor 20% albumin) were introduced sequentially to 760 patients in an intensive care unit (ICU) setting after a 6-month washout period. The results showed significantly less AKI with the use of balanced solutions. The 0.9% Saline vs. Plasma-Lyte 148 for Intensive Care Fluid Therapy (SPLIT) trial was published 3 years later in 2015 by Young et al. (5) in an ICU setting. This was the first blind randomized clinical trial (RCT), to our knowledge, and did not report any significant difference in the incidence of AKI, kidney replacement therapy (KRT) use, and in-hospital mortality between balanced and saline solutions in the ICU setting.

Large, pragmatic trials

The Isotonic Solutions and Major Adverse Renal Events Trial (SMART) (6) was a single-center, cluster-randomized, multiple cross-over, pragmatic study conducted in an ICU setting in which over 15,000 adults either received 0.9% saline or balanced crystalloids during their stay in the ICU. Major adverse kidney events within 30 days (MAKE-30; i.e., a composite of death, need for new KRT, and persistent kidney dysfunction at 30 days) were assessed in both groups. An absolute difference of 1.1% in MAKE-30 (14.3% in the balanced group versus 15.4% in the saline group) was obtained between the groups, which was statistically significant (p = 0.04)

The Saline against Lactated Ringers or Plasmalyte in the Emergency Department (SALT-ED) trial (7) included more than 13,000 non-critically ill patients from the same single center as SMART. Although the primary outcome of hospital-free days did not differ between the groups receiving 0.9% saline or balanced crystalloids, the secondary outcome of MAKE-30 was significantly less (p = 0.01) in the balanced crystalloid group. Furthermore, the difference in MAKE-30 appeared to be highest in patients with hyperchloremia or an elevated plasma creatinine value at presentation.

. . . only in recent years has normal saline been under the spotlight with several studies questioning whether this is the best solution to use.

The limitations of SMART and the SALT-ED trial included the open-label nature, involvement of only a single

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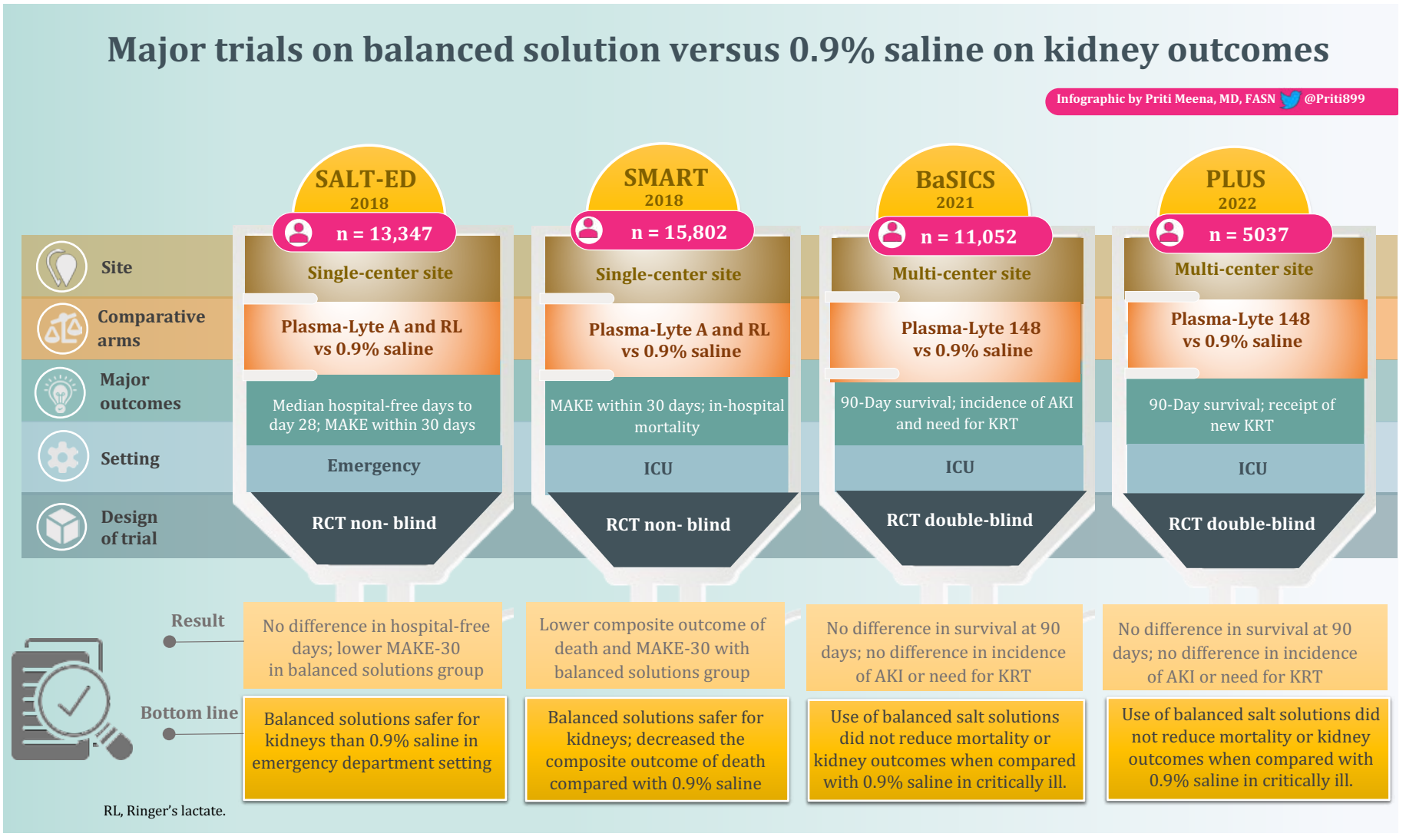

Balanced Salt Solutions

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center, and the decision to start KRT based on individual clinician preference, which had implications in the final outcomes.

New entries into the debate

The Balanced Solution Versus Saline in Intensive Care Study (BaSICS) trial, published in 2021 by Zampieri et al. (8) was a multi-center, double-blind RCT conducted in 75 ICUs in Brazil and randomized approximately 11,000 patients to balanced crystalloids or saline groups. The researchers found that at 90 days, there was no difference in death with either strategy. The secondary outcomes, such as incidence of AKI and need for KRT, were also not statistically different. This lack of difference was despite achieving significantly less chloride levels in the balanced crystalloids group.

The Plasma-Lyte 148® Versus Saline Study (PLUS) trial of 2022 (9) is the latest publication, to our knowledge, to address this debate about use of balanced crystalloids or saline. More than 5000 people were randomized to receive balanced crystalloids versus saline in multiple centers as a part of this double-blind RCT. In this study, 90 days' mortality, start of KRT, and increased creatinine were similar between both groups. Despite achieving lower chloride levels, the balanced crystalloid group did not demonstrate less mortality or reduced kidney injury.

The limitations of the BaSICS and PLUS trials included the use of non-study fluids for drugs and infusion, which may have led to some degree of contamination. Fluids were administered before randomization, and many participants in both the balanced crystalloids and saline groups were elective surgical patients, which may have reduced overall mortality.

A meta-analysis by Hammond et al. in 2022 (10) used data from the BaSICS and PLUS trials and 11 other RCTs. This analysis showed that with a low risk of bias among these studies, there was a reduction in relative risk of both mortality and AKI in a heterogenous group receiving balanced solutions.

Conclusions

Today, we have two more multi-centric RCTs (8, 9) that do not reiterate the findings of their predecessors and have gone on to demonstrate no such benefit when balanced salt solutions are used. However, a meta-analysis and systemic review (10) of 13 previously published RCTs in this field did show risk reduction with use of balanced solutions. So, where do we stand now with all of this evidence?

Some common points across these trials are that the use of balanced salt solutions was detrimental in patients with traumatic brain injury and caused higher mortality. Saline also remains an intuitive choice in cases of hypovolemic hyponatremia or hypochloremic metabolic alkalosis. Furthermore, the compatibility of balanced solutions with various drugs is not clear, and saline may be preferred for these purposes. The cost also needs to be recognized, considering the massive quantities of all fluids (especially plasmalyte) used.

Considering recent and past studies, we may be able to conclude that in patients without any baseline or impending kidney dysfunction, choice of fluid may not affect kidney outcomes. However, in patients with increased creatinine, acidosis, and hyperchloremia or with impending kidney injury, moving to a balanced solution strategy may be justified to reduce adverse kidney-related events. ■

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The authors report no conflicts of interest.

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