

Kidney News

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CKD Patients Starting Dialysis “Late” Fare No Worse than Those Starting Early



Planned early initiation of dialysis does not improve survival for patients with stage 5 chronic kidney disease, a new study finds.

Early dialysis start times did not result in fewer cardiovascular, infectious disease, or dialysis-related complications in the eight-year trial titled Initiating Dialysis Early and Late (IDEAL). Results from the prospective, randomized multicenter controlled clinical trial were published by the *New England Journal of Medicine* and presented at the European Renal Association-European Dialysis and Transplant Association 2010 Congress in June.

The study population included 828 patients over 18 years at 32 centers in Australia and New Zealand. The patients were randomly assigned to one of two groups: “early start” and “late start.” The protocol for the “early start” group called for starting dialysis when the patients’ estimated glomerular filtration rate (eGFR) was 10–14 mL per minute. In the “late start” group, dialysis was planned to occur when the eGFR fell to 5–7 mL per minute.

The IDEAL investigators reported that death from any cause—which was the primary study outcome—occurred in 152 (37.6 percent) of the 404 patients in the “early start” group and 155 (36.6 percent) of the “late start” patients. Incidence of infections and other complications did not differ between the two groups.

Our results indicate that . . . trends toward early initiation of dialysis, which have enough implications in terms of cost and infrastructure of dialysis services, are unlikely to improve clinical outcomes,” wrote IDEAL investigators Bruce A. Cooper, PhD, of Royal North Shore Hospital and Sydney Medical School in Sydney, Australia, and the lead author of the *NEJM* paper.

The trial’s findings highlight the importance of clinical symptoms and patient follow-up in determining the onset of dialysis.

“In our view, the IDEAL trial supports the currently recommended practice in which most nephrologists start patients on renal replacement therapy

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CMS Finalizes New ESRD Bundled Payment System

By Rachel Shaffer

Fundamentally changing how Medicare pays for dialysis services for patients with end stage renal disease (ESRD), the Centers for Medicare and Medicaid Services (CMS) released the Final ESRD Prospective Payment System (PPS) Rule in late July. Under the new “bundled” payment system, effective January 1, 2011, Medicare will provide a single payment that covers all renal dialysis

services—including drugs and diagnostic laboratory tests—to dialysis facilities for each dialysis treatment. Medicare currently pays facilities a composite rate for most items and services, while paying separately for certain drugs, laboratory tests, and other services.

Simultaneously, CMS issued a proposed rule that will establish a new quality incentive program (QIP) for facilities that

provide renal dialysis services (see sidebar). The QIP is the first pay-for-performance program in a Medicare fee-for-service program. Currently, facilities only report on whether they have complied with quality measures. Beginning in 2012, the extent to which dialysis facilities meet established performance standards will be reflected in their payment rates, with reductions of up to 2 percent.

The new ESRD payment system is historic for two reasons: It is the first bundled payment system of its kind CMS has implemented, and it marks the first time Medicare will vary payment based on the quality of care. These features—bundled

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Renvela® (sevelamer carbonate) tablets or for oral suspension is an effective first-line monotherapy for controlling serum phosphorus in dialysis patients — without calcium or metal¹ accumulation. Renvela is the **only** phosphate binder available in both tablet and powder dosing options.



Learn more about Renvela powder at renvela.com.



Indication: Renvela® (sevelamer carbonate) is indicated for the control of serum phosphorus in patients with chronic kidney disease (CKD) on dialysis.

Important Treatment Considerations

Renvela is contraindicated in patients with bowel obstruction • Caution should be exercised in patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders including severe constipation, or major GI tract surgery • Uncommon cases of bowel obstruction and perforation have been reported • Serum bicarbonate and chloride levels should be monitored • Vitamins D, E, K (coagulation parameters), and folic acid levels should be monitored • The most frequently occurring adverse reactions in a short-term study with sevelamer carbonate tablets were nausea and vomiting • In a short-term study of sevelamer carbonate powder dosed three times daily, adverse events were similar to those reported for sevelamer carbonate tablets • In long-term studies with sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, the most common adverse events included: vomiting, nausea, diarrhea, dyspepsia, abdominal pain, flatulence, and constipation • Cases of fecal impaction and, less commonly, ileus, bowel obstruction, and bowel perforation have been reported • Drug-drug interactions may occur with some medications and should be taken into consideration when instructing patients how to take Renvela • Patients should be informed to take Renvela with meals and to adhere to their prescribed diets

Please see Brief Summary of Prescribing Information on adjacent page.

Reference: 1. Renvela [package insert]. Cambridge, MA: Genzyme Corp; 2009.

CKD Patients

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on the basis of clinical factors rather than numerical criteria such as the estimated GFR alone,” wrote the authors of an editorial published along with the paper. Norbert Lameire, MD, PhD, and Wim Van Biesen, MD, PhD, of the University Hospital Ghent, University of Ghent, Belgium, authored the editorial.

That clinical factors, not just a pre-determined GFR, should influence decision-making was emphasized by Ra-

jnish Mehrotra, MD, who chairs ASN’s Dialysis Advisory Group, and National Kidney Foundation President Bryan N. Becker, MD.

“The IDEAL results provide several lessons: delaying dialysis till the appearance of symptoms does no harm, contrary to the previous nonrandomized studies; beginning dialysis early also does no harm; and the traditional clinical criteria, patient monitoring and follow-up appear to be more important than the actual level of renal function in deciding when dialysis should begin,” said Mehrotra,

professor of medicine at UCLA’s David Geffen School of Medicine and associate chief and of the division of nephrology and Hypertension at Harbor-UCLA Medical Center.

“In my view, the single biggest aspect of the IDEAL trial was that because of uremia, fluid overload, or other symptoms, over 75 percent of the patients in the “late start” group began dialysis when their GFR was above the study’s target of 7.0 mL per minute,” said Becker, professor of medicine at the University of Wisconsin School of Medicine and

Public Health. Becker also is physician-in-chief and head of the section of nephrology.

As a result, the mean eGFR at the start of dialysis in the “late start” group was 9.8 mL/min/1.73 m². The median time to the initiation of dialysis was 7.4 months in this group versus 1.8 months in the “early start” group. The study protocol allowed patients assigned to “late start” to begin dialysis early at the recommendation of the treating physician, who was not required to discuss this decision in advance with the trial coordinator.

Becker applauded the extensive patient follow-up, repeated contact, and patient education provided to the chronic kidney disease patients in the IDEAL study, and noted that this high level of care may have influenced the similar outcomes of the “early start” and “late start” groups.

“The vast majority of patients in the study were instructed about chronic kidney disease and the potential need for dialysis,” he said. “One manifestation of the preparation was that dialysis access was already in place before it became evident that the patient would need dialysis.” IDEAL did not require the treating physicians to place a temporary catheter to avoid delaying the assigned start time. Decisions about temporary placement were based on clinical judgment.

In the real world of clinical medicine in the United States, nephrologists too often do not have the opportunity to educate and prepare patients well in advance of initiating dialysis.

“In the IDEAL study cohort, the patients were seeing a nephrologist for about two and one-half years before beginning dialysis,” Mehrotra said. “In the United States, over 40 percent of the 110,000 patients who begin dialysis each year have had no pre-dialysis care by a nephrologist.”

The patient care provided to the IDEAL participants and to most U.S. chronic kidney disease patients differs in other respects, Mehrotra said. While 7 percent of U.S. patients are on peritoneal dialysis, 57.7 percent and 54.9 percent of the “early start” and “late start” groups were on peritoneal dialysis, respectively. In the IDEAL study, a temporary dialysis catheter was used in 5 percent of the patients. About 80 percent of kidney disease patients begin dialysis with a catheter in the United States.

The IDEAL results challenge the worldwide trend toward early renal replacement therapy. From 1996 to 2005, the proportion of patients in whom dialysis was initiated when the eGFR was greater than 10 mL per minute increased from 19 percent to 45 percent, according to the U.S. Renal Data System.

Mehrotra noted that patients who begin dialysis when their eGFR is relatively high usually are “the sickest patients. They are the most likely to be diabetic or have a history of congestive heart failure.”

Continued on page 4

Renvela[®]

sevelamer carbonate

[se vel' a mer]

See package insert for full prescribing information.

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Renvela[®] (sevelamer carbonate) is indicated for the control of serum phosphorus in patients with chronic kidney disease (CKD) on dialysis.

DOSAGE AND ADMINISTRATION

Because of the rapid reaction with the hydrochloric acid in the stomach, the dosing of Renvela powder or tablet is anticipated to be similar to that of the sevelamer hydrochloride salt or tablet.

General Dosing Information

Patients Not Taking a Phosphate Binder. The recommended starting dose of Renvela is 0.8 to 1.6 g, with meals based on serum phosphorus level. Table 1 provides recommended starting doses of Renvela for patients not taking a phosphate binder.

Table 1. Starting Dose for Dialysis Patients Not Taking a Phosphate Binder

SERUM PHOSPHORUS	RENVELA [®] 800 MG	RENVELA POWDER
> 5.5 and < 7.5 mg/dL	1 tablet three times daily with meals	0.8 g three times daily with meals
> 7.5 mg/dL	2 tablets three times daily with meals	1.6 g three times daily with meals

Switching from Sevelamer Hydrochloride Tablets. For patients switching from sevelamer hydrochloride tablets to sevelamer carbonate tablets or powder, use the same dose in grams. Further titration may be necessary to achieve desired phosphorus levels. The highest daily dose of sevelamer carbonate studied was 14 grams in CKD patients on dialysis.

Switching between Sevelamer Carbonate Tablets and Powder. Use the same dose in grams. Further titration may be necessary to achieve desired phosphorus levels.

Switching from Calcium Acetate. In a study in 84 CKD patients on hemodialysis, a similar reduction in serum phosphorus was seen with equivalent doses (approximately mg for mg) of sevelamer hydrochloride and calcium acetate. Table 2 gives recommended starting doses of Renvela based on a patient's current calcium acetate dose.

Table 2. Starting Dose for Dialysis Patients Switching From Calcium Acetate to Renvela

CALCIUM ACETATE 667 MG (TABLETS PER MEAL)	RENVELA [®] 800 MG (TABLETS PER MEAL)	RENVELA POWDER
1 tablet	1 tablet	0.8 g
2 tablets	2 tablets	1.6 g
3 tablets	3 tablets	2.4 g

Dose Titration for All Patients Taking Renvela. Titrate the Renvela dose by 0.8 g TID with meals at two-week intervals as necessary with the goal of controlling serum phosphorus within the target range.

Sevelamer Carbonate Powder Preparation Instructions

The entire contents of each 0.8 or 2.4 g packet should be placed in a cup and mixed thoroughly with the amount of water described in Table 3.

Table 3. Sevelamer Carbonate Powder Preparation Instructions

RENVELA POWDER PACKET STRENGTH	MINIMUM AMOUNT OF WATER FOR DOSE PREPARATION (EITHER OUNCES, mL, OR TEASPOON/TABLESPOON)		
	ounces	mL	tsp/tbsp
0.8 g	1	30	6 teaspoons/2 tablespoons
2.4 g	2	60	4 tablespoons

Multiple packets may be mixed together with the appropriate amount of water. Patients should be instructed to stir the mixture vigorously (it does not dissolve) and drink the entire preparation within 30 minutes or resuspend the preparation right before drinking.

Based on clinical studies, the average prescribed daily dose of sevelamer carbonate is approximately 7.2 g per day.

DOSAGE FORMS AND STRENGTHS

Tablets: 800 mg white oval, film-coated, compressed tablets imprinted with "RENVELA 800".

Powder: 0.8 g and 2.4 g pale yellow powder packaged in an opaque, foil lined, heat sealed packet.

CONTRAINDICATIONS

Renvela is contraindicated in patients with bowel obstruction.

WARNINGS AND PRECAUTIONS

Use Caution in Patients with Gastrointestinal Disorders. The safety of Renvela has not been established in patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders including severe constipation, or major GI tract surgery. Uncommon cases of bowel obstruction and perforation have been reported.

Monitor Serum Chemistries. Bicarbonate and chloride levels should be monitored.

Monitor for Reduced Vitamins D, E, K (clotting factors) and Folic Acid Levels. In preclinical studies in rats and dogs, sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, reduced vitamins D, E, and K (coagulation parameters) and folic acid levels at doses of 6–10 times the recommended human dose. In short-term clinical trials, there was no evidence of reduction in serum levels of vitamins. However, in a one-year clinical trial, 25-hydroxyvitamin D (normal range 10 to 55 ng/mL) fell from 39 ± 22 ng/mL to 34 ± 22 ng/mL (p<0.01) with sevelamer hydrochloride treatment. Most (approximately 75%) patients in sevelamer hydrochloride clinical trials received vitamin supplements, which is typical of patients on dialysis.

ADVERSE REACTIONS

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

There are limited data on the safety of Renvela. However, based on the fact that it contains the same active ingredient as the hydrochloride salt, the adverse event profiles of the two salts should be similar. In a cross-over study in hemodialysis patients with treatment durations of eight weeks each and no washout between treatment periods, adverse reactions to sevelamer carbonate tablets were similar to those reported for sevelamer hydrochloride. In another cross-over study in hemodialysis patients, with treatment durations of four weeks each and no washout between treatment periods, the adverse reactions to sevelamer carbonate powder were similar to those reported for sevelamer hydrochloride.

In a parallel design study of sevelamer hydrochloride with treatment duration of 52 weeks, adverse reactions reported for sevelamer hydrochloride (n=99) were similar to those reported for the active-comparator group (n=101). Overall adverse reactions among those treated with sevelamer hydrochloride occurring in > 5% of patients included: vomiting (22%), nausea (20%), diarrhea (19%), dyspepsia (16%), abdominal pain (9%), flatulence (8%), and constipation (8%). A total of 27 patients treated with sevelamer and 10 patients treated with comparator withdrew from the study due to adverse reactions.

Based on studies of 8–52 weeks, the most common reason for withdrawal from sevelamer hydrochloride was gastrointestinal adverse reactions (3–16%).

In one hundred and forty-three peritoneal dialysis patients studied for 12 weeks using sevelamer hydrochloride, most adverse reactions were similar to adverse reactions observed in hemodialysis patients. The most frequently occurring treatment emergent serious adverse reaction was peritonitis (8 reactions in 6 patients [8%] in the sevelamer group and 2 reactions in 2 patients [4%] on active-control). Thirteen patients (14%) in the sevelamer group and 9 patients (20%) in the active-control group discontinued, mostly for gastrointestinal adverse reactions. Patients on peritoneal dialysis should be closely monitored to ensure the reliable use of appropriate aseptic technique with the prompt recognition and management of any signs and symptoms associated with peritonitis.

Postmarketing Experience: Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure.

The following adverse reactions have been identified during post-approval use of sevelamer hydrochloride, which has the same active moiety as sevelamer carbonate: pruritus, rash, abdominal pain, fecal impaction, and uncommon cases of ileus, intestinal obstruction, and intestinal perforation. Appropriate medical management should be given to patients who develop constipation or have worsening of existing constipation to avoid severe complications.

DRUG INTERACTIONS

Sevelamer carbonate has been studied in human drug-drug interaction studies with warfarin and digoxin. Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, has been studied in human drug-drug interaction studies with ciprofloxacin, digoxin, warfarin, enalapril, metoprolol, and iron.

Ciprofloxacin: In a study of 15 healthy subjects, a co-administered single dose of 2.8 grams of sevelamer hydrochloride decreased the bioavailability of ciprofloxacin by approximately 50%.

Digoxin: In 19 healthy subjects receiving 2.4 grams of sevelamer hydrochloride three times a day with meals for 2 days, sevelamer did not alter the pharmacokinetics of a single dose of digoxin. In 18 healthy subjects receiving 9.6 grams of sevelamer carbonate once daily, sevelamer did not alter the pharmacokinetics of a single dose of digoxin.

Warfarin: In 14 healthy subjects receiving 2.4 grams of sevelamer hydrochloride three times a day with meals, sevelamer did not alter the pharmacokinetics of a single dose of warfarin. In 14 healthy subjects receiving 9.6 grams of sevelamer carbonate once daily with meal, sevelamer did not alter the pharmacokinetics of a single dose of warfarin.

Enalapril: In 28 healthy subjects a single 2.4 gram dose of sevelamer hydrochloride did not alter the pharmacokinetics of a single dose of enalapril.

Metoprolol: In 31 healthy subjects a single 2.4 gram dose of sevelamer hydrochloride did not alter the pharmacokinetics of a single dose of metoprolol.

Iron: In 23 healthy subjects, a single 2.8 gram dose of sevelamer hydrochloride did not alter the absorption of a single oral dose of iron as 200 mg exsiccated ferrous sulfate tablet.

Other Concomitant Drug Therapy: There are no empirical data on avoiding drug interactions between Renvela and most concomitant drugs. During postmarketing experience, very rare cases of increased thyroid stimulating hormone (TSH) levels have been reported in patients co-administered sevelamer hydrochloride and levothyroxine. Monitor TSH levels and signs of hypothyroidism in patients receiving both medications.

When administering an oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, there is no information suggesting a dosing regimen that would be universally appropriate for all drugs. One may, however, administer the drug one hour before or three hours after Renvela, and when important, monitor blood levels of the drug. Patients taking anti-arrhythmic medications for the control of arrhythmias and anti-seizure medications for the control of seizure disorders were excluded from the clinical trials.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Sevelamer products should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The effect of sevelamer hydrochloride on the absorption of vitamins and other nutrients has not been studied in pregnant women. Requirements for vitamins and other nutrients are increased in pregnancy. In pregnant rats given doses of sevelamer hydrochloride during organogenesis, reduced or irregular ossification of fetal bones, probably due to a reduced absorption of fat-soluble vitamin D, occurred at a dose approximately equal to the maximum clinical trial dose of 13 g on a body surface area basis. In pregnant rabbits given oral doses of sevelamer hydrochloride by gavage during organogenesis, an increase of early resorptions occurred at a dose approximately twice the maximum clinical trial dose on a body surface area basis. (See *NONCLINICAL TOXICOLOGY* (13.2)).

Labor and Delivery: No sevelamer hydrochloride treatment-related effects on labor and delivery were seen in animal studies (See *NONCLINICAL TOXICOLOGY* (13)). The effects of sevelamer carbonate on labor and delivery in humans is unknown.

Pediatric use: The safety and efficacy of Renvela has not been established in pediatric patients.

Geriatric use: Clinical studies of Renvela did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.

OVERDOSAGE

Sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, has been given to normal healthy volunteers in doses of up to 14 grams per day for eight days with no adverse effects. In CKD patients on dialysis, the maximum dose studied was 14 grams of sevelamer carbonate and 13 grams of sevelamer hydrochloride. There are no reports of overdosage with sevelamer carbonate or sevelamer hydrochloride in patients. Since sevelamer is not absorbed, the risk of systemic toxicity is low.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Rats were given sevelamer hydrochloride by diet at 0.3, 1, or 3 g/kg/day. There was an increased incidence of urinary bladder transitional cell papilloma in male rats of the high dose group (human equivalent dose twice the maximum clinical trial dose of 13 g). Mice received dietary administration of sevelamer hydrochloride at doses of up to 9 g/kg/day (human equivalent dose 3 times the maximum clinical trial dose). There was no increased incidence of tumors observed in mice.

In an *in vitro* mammalian cytogenetic test with metabolic activation, sevelamer hydrochloride caused a statistically significant increase in the number of structural chromosome aberrations. Sevelamer hydrochloride was not mutagenic in the Ames bacterial mutation assay.

Sevelamer hydrochloride did not impair the fertility of male or female rats in a dietary administration study in which the females were treated from 14 days prior to mating through gestation and the males were treated for 28 days prior to mating. The highest dose in this study was 4.5 g/kg/day (human equivalent dose 3 times the maximum clinical trial dose of 13 g).

Developmental Toxicity: In pregnant rats given dietary doses of 0.5, 1.5, or 4.5 g/kg/day of sevelamer hydrochloride during organogenesis, reduced or irregular ossification of fetal bones, probably due to a reduced absorption of fat-soluble vitamin D, occurred in mid- and high-dose groups (human equivalent doses approximately equal to and 3.4 times the maximum clinical trial dose of 13 g). In pregnant rabbits given oral doses of 100, 500, or 1000 mg/kg/day of sevelamer hydrochloride by gavage during organogenesis, an increase of early resorptions occurred in the high-dose group (human equivalent dose twice the maximum clinical trial dose).

HOW SUPPLIED/STORAGE AND HANDLING

Tablets: Renvela[®] 800 mg Tablets are supplied as white oval, film-coated, compressed tablets, imprinted with "RENVELA 800", containing 800 mg of sevelamer carbonate on an anhydrous basis, microcrystalline cellulose, hypromellose, diacetylated monoglycerides, sodium chloride, and zinc stearate.

1 Bottle of 30 ct 800 mg Tablets (NDC 58468-0130-2)

1 Bottle of 270 ct 800 mg Tablets (NDC 58468-0130-1)

Powder: Renvela[®] for Oral Suspension is supplied as opaque, foil lined, heat sealed, packets containing 0.8 g or 2.4 g of sevelamer carbonate on an anhydrous basis, natural and artificial citrus cream flavor, propylene glycol alginate, sodium chloride, sucralose, and ferric oxide (yellow).

1 Box (NDC 58468-0131-2) of 90 ct 2.4 g packets (NDC 58468-0131-1)

1 Box (NDC 58468-0132-2) of 90 ct 0.8 g packets (NDC 58468-0132-1)

1 Sample Box (NDC 58468-0131-4) of 90 ct 2.4 g packets (NDC 58468-0131-3)

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CKD Patients

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Launched in 2000, IDEAL recruited chronic kidney disease patients whose estimated GFR was 10–15 mL/min/1.73 m² of body-surface area, as calculated by using the Cockcroft–Gault equation. The 32 centers included rural and urban, as well as general and university hospital settings.

ESRD Bundled Payment System

Continued from page 1

services and pay-for-performance—are likely to be increasingly prevalent within the Medicare reimbursement system in coming years. Indeed, health reform legislation instructs the Department of Health and Human Services (HHS) to pilot multiple versions of bundled payment systems. “The new payment system and quality incentive program for dialysis services have significant potential to improve patient outcomes and promote efficient delivery of health care services,” said CMS Administrator Donald Berwick, MD. Demonstrating the effects of bundled payments for care of patients with chronic disease, implementation of the ESRD PPS may well act as a model for future health care payment reforms.

The ASN Public Policy Board, ESRD Task Force, and policy staff analyzed and commented extensively upon the ESRD PPS Proposed Rule in 2009. The final rule addressed many of the concerns ASN conveyed to CMS during the comment period. Creating separate payments for home dialysis training, preserving physician flexibility in ordering lab tests and medications, monitoring the bundle’s influence on patient care and access, and evaluating the effect of new copayments on patients are among the many revisions CMS made to its proposals following ASN’s comments.

Currently, these ASN groups are conducting an in-depth review of the final rule, which is not open for public comment. This summary presents an overview of several of the most significant provisions in the Rule. Over the coming weeks and months ASN will continue working to help members understand how medical practice and patient care will be affected by these changes. The society will also be working closely with CMS as a liaison between the agency and the nephrology community.

Scope of the bundle: oral-only drugs

In the final rule, CMS finalizes its proposal to make a single bundled payment to dialysis facilities for each dialysis treatment that covers all dialysis-related drugs, diagnostic laboratory tests, equipment, supplies and staff time. For 2011, CMS sets the standardized base rate of the bundle at \$229.63, which will be multiplied by patient and facility-level payment adjusters. As CMS proposed in 2009, the bundle will include erythropoiesis-stimulating agents (ESAs) and “oral-only ESRD-related drugs and biologicals.”

The study ended in 2008 and followed patients for an additional year.

Although the dialysis method was specified for each patient before randomization, the treating physician and the patient ultimately determined the method and regimen.

“As the National Kidney Foundation goes through its traditional guideline assessment, certainly we’ll want to see the IDEAL data represented,” said Becker. ●

However, CMS will not add oral-only medications to the bundle until January 1, 2014. Patients will continue to have access to these products under Medicare Part D until that date.

This delay period will enable CMS to address many of the concerns raised by ASN in its comment on the Proposed Rule about ESRD facilities’ ability to furnish drugs formerly covered under Part D, as well as the CMS’s ability to identify and remediate any negative changes in availability or quality of patient care. Among other things, the delay will allow:

- CMS time to conduct additional analysis regarding the ability of ESRD facilities to provide oral-only ESRD drugs.
- ESRD facilities time to develop the arrangements or infrastructure necessary to provide oral-only drugs and negotiate prices with drug companies.
- CMS time for additional analysis of ESRD facilities’ ability to provide oral-only ESRD drugs.
- CMS time to evaluate the need for additional clinical indicators applicable to the monitoring of certain patient conditions treated with oral-only drugs, such as bone loss and mineral metabolism associated with the provision of calcimimetics and phosphate binders. This could assist in determining the impact of the fully bundled payment system—and any unintentional consequences that might ensue—on quality of care.

Scope of the bundle: oral drugs with an injectable equivalent

CMS will include oral drugs with an injectable equivalent in the bundle beginning January 1, 2011. CMS classifies these products into five ESRD drug categories based on mechanism of action, and envisions that these categories will provide flexibility to incorporate new products into the bundle as they become available in the future. The final rule also delineates several drug categories expressly excluded from the base rate, which CMS will continue to bill separately. These include drugs and biologicals classified as immunosuppressant drugs, vaccines, and chemotherapeutic drugs. The final rule, which is accessible on ASN’s website, contains a complete list of these drugs.

Responding directly to ASN’s comment that many nephrologists serve as primary care providers for their patients and in this capacity sometimes need to prescribe non-ESRD-related drugs, CMS ruled that nephrologists may continue to order such products in the new payment environment. The agency created a new modifier on the claim form for this purpose. CMS also identifies a small number of products that are sometimes ESRD-related but are also often prescribed for other

reasons. Facilities will be eligible to receive separate payment for these products, using the same new modifier to indicate the drug was not administered for ESRD care.

Diagnostic laboratory tests

CMS also addressed ASN’s concerns that nephrologists continue to be able to order laboratory values that are not related to renal dialysis services. Allowing MCP nephrologists to order such laboratory tests minimizes patient discomfort, protects vascular access, and enables nephrologists to serve as primary care providers. CMS adopted ASN’s recommendation to identify non-ESRD-related lab tests by using another separate modifier that allows for a separate payment for those tests. As such, CMS compiled a list of 53 lab tests used to diagnose or monitor ESRD-related conditions (Table 1). Only tests included on this list will be paid under the bundle. CMS notes that the list was compiled based on tests most frequently identified by commenters as ESRD-related, input from physicians at the University of Michigan Kidney Epidemiology and Cost Center, and a medical review by CMS physicians and other staff.

Patient-level adjustors

In the final rule, CMS adopts four patient-level case-mix payment adjustors—for age, body mass index, body surface area, and new patients—as well as six co-morbidity categories (listed below) for the co-morbidity case-mix adjustment.

- pericarditis (acute)
- bacterial pneumonia (acute)
- gastrointestinal tract bleeding with hemorrhage (acute)
- hemolytic anemia with sickle cell anemia (chronic)
- myelodysplastic syndrome (chronic)
- monoclonal gammopathy (chronic)

CMS originally proposed including an adjustor for patient sex and for race/ethnicity, but at this time is not finalizing its proposals for these characteristics. ASN had expressed concern that the data employed to determine patient-level case-mix adjustors may not be complete or may not capture the most costly variables in patient care. Stating in the final rule that it is updating processes for collecting and validating patient-level data, CMS will continue studying patient sex and race/ethnicity. The agency also intends to perform additional studies to determine whether there are underlying clinical or biological factors

contributing to the increased cost of providing care to certain groups. As it weighs decisions on the patient sex and race/ethnicity adjustors, CMS said it will continue to monitor for evidence of decreased access to renal dialysis services—a key activity ASN emphasized the agency conduct in the new payment environment.

Co-payments

Under the ESRD PPS, the beneficiary’s coinsurance amount will be 20 percent of the ESRD PPS bundled payment amount, including applicable case-mix and facility-level adjustments and outlier payments. Patients accessing care at facilities undergoing the four-year transition period will pay coinsurance on 20 percent of the blended payment amount.

Under the existing payment system, patients are not responsible to pay coinsurance on laboratory services, but will become subject to the 20 percent coinsurance obligation when the services are bundled into the set of renal dialysis services on January 1, 2011. Similarly, drugs being bundled that are currently payable under Medicare Part D—and currently subject to a separate coinsurance structure—will be subject to the 20 percent coinsurance part of the set of bundled renal dialysis services.

Importantly, however, oral-only ESRD drugs will not immediately be among the products for which patients are responsible to pay coinsurance—CMS will continue to pay these drugs under Part B until January 1, 2014, when CMS adds them to the bundle. ASN voiced concerns about the new financial burden created for patients by adding drugs that were formerly payable under Part D to the bundle. In response, CMS stated in the final rule that it plans to collect data on the oral-only ESRD drugs to assess the impact on beneficiaries and facilities. The agency will address the implementation of oral-only drugs in a future notice of proposed rulemaking.

The new base rate reflects the average cost for furnishing dialysis services to patients. For this reason, CMS said, if patients today use less than the average of separately billable items and services (that is, items and services that were separately paid under the current basic case-mix adjusted composite payment system), they can expect an increase in their co-insurance obligation. However, if patients currently use more than the average of separately billable items and services, they should pay less in co-insurance under the new bundled payment system. The amount of the difference

in co-insurance under the current payment system and the new bundled payment system for an individual patient is directly related to how their use of separately billable services compares to the average amount.

Home dialysis

As encouraged by ASN and others, CMS adopts a payment adjustor for home dialysis training for both hemodialysis and peritoneal dialysis (PD) modalities. The agency will provide this add-on adjustment to facilities each time they conduct home dialysis training, rather than accounting for the cost of home training in the base rate applied to all facilities, as CMS originally proposed. However, facilities are not eligible to receive the home dialysis training add-on during the first four months after initiating dialysis while the new-patient adjustor is in effect.

Transition period

The final rule includes a four-year phase-in (transition) of bundled payments, with the phase-in occurring in equal increments until 2014, when 100 percent of ESRD services will be covered under the bundle. In 2011, 75 percent of the transition will be based on the payment rate under the current basic case-mix adjusted composite payment system and 25 percent based on the new bundled ESRD PPS payment amount. In 2012, the balance will be 50-50, and in 2013, 25 percent of the transition will be based on the payment rate under the current basic case-mix adjusted composite payment system and 75 percent based on the new bundled ESRD PPS payment amount. Dialysis facilities have until November 1, 2010, to make a one-time selection to be excluded from the transition and paid entirely under the new fully bundled system as of January 1, 2011.

Physician services

CMS states in the final rule that it does not, at this time, intend to modify payment for physicians’ services. The agency is limiting the scope of this rulemaking to payment for dialysis services, and notes that any changes in payment for physician services would be addressed in future rulemaking.

ASN thanks the members of the Policy Board and ESRD Task Force for their contributions on behalf of the society.

Table 1. Lab tests used to diagnose or monitor ESRD-related conditions that will be paid under the bundle

CPT	HCPCS Short description
82040	Assay of serum albumin
82108	Assay of aluminum
82306	Vitamin D, 25 hydroxy
82310	Assay of calcium
82330	Assay of calcium, ionized
82374	Assay, blood carbon dioxide
82379	Assay of carnitine
82435	Assay of blood chloride
82565	Assay of creatinine
82570	Assay of urine creatinine
82575	Creatinine clearance test
82607	Vitamin B-12
82652	Vit D 1, 25-dihydroxy
82668	Assay of erythropoietin
82728	Assay of ferritin
82746	Blood folic acid serum
83540	Assay of iron
83550	Iron binding test
83735	Assay of magnesium
83970	Assay of parathormone
84075	Assay alkaline phosphatase
84100	Assay of phosphorus
84132	Assay of serum potassium
84134	Assay of prealbumin
84155	Assay of protein, serum
84295	Assay of serum sodium
84466	Assay of transferrin
84520	Assay of urea Nitrogen
84540	Assay of urine/urea-N
84545	Urea-N clearance test
85014	Hematocrit
85018	Hemoglobin
85025	Complete (CBC), automated (Hgb, Hct, RBC, WBC, and Platelet count) and automated differential WBC count
85027	Complete (CBC), automated (Hgb, Hct, RBC, WBC, and Platelet count)
85041	Automated RBC count
85044	Manual reticulocyte count
85045	Automated reticulocyte count
85046	Reticyte/Hgb concentrate
85048	Automated leukocyte count
86704	Hep B core antibody, total
86705	Hep B core antibody, IgM
86706	Hep B surface antibody
87040 ¹	Blood culture for bacteria
87070 ¹	Culture, bacteria, other
87071 ¹	Culture bacteria aerobic other
87073 ¹	Culture bacteria anaerobic
87075 ¹	Culture bacteria, except blood
87076 ¹	Culture anaerobe ident, each
87077 ¹	Culture aerobic identify
87081 ¹	Culture screen only
87340	Hepatitis B surface Ag, eia
G0306	CBC/diff WBC w/o platelet
G0307	CBC without platelet

¹ Only ESRD-related when testing is related to the dialysis access site.

CMS Proposes Quality Incentive Program

Besides implementing a bundled payment system for ESRD care, CMS outlined its vision for a Quality Improvement Program (QIP) in a Proposed Rule, released the same day as the ESRD Final Rule. The QIP will be the first pay-for-performance program in a Medicare fee-for-service payment program and will go into effect on January 1, 2012. The proposed rule is open for comment until September 24, 2010.

Intended to improve outcomes for ESRD patients, the QIP will adjust dialysis facility payments based on facilities’ performance across three quality measures—with a reduction of up to 2 percent for facilities that do not meet or exceed the standards. The three quality measures are:

- hemodialysis adequacy: Achieved urea reduction ratio of 65 percent or more
- anemia management: Controlled anemia, as shown in two measures:
 - o percentage of patients at a facility whose hemoglobin levels were less than 10 g/dL
 - o percentage of patients at a facility whose hemoglobin levels were greater than 12 g/dL

Facilities have already been reporting these measures on claims, and the results for each facility are publicly available on the CMS Dialysis Facility Compare website. Having finalized the quality measures for the QIP in the ESRD Final Rule, CMS addresses other aspects of the QIP in the proposed rule. Besides selecting performance standards against which facilities will be judged, the agency proposes a sliding scale for reducing payment rates based on a total performance score that reflects all three measures. Although the payment reductions will not take place until January 2012, CMS states that the performance period must occur before that date to allow for claims processing. CMS proposes a performance period for the entire calendar year of 2010.

ASN has formed a QIP Task Force to analyze the proposed rule and provide comment to CMS, in conjunction with the ASN Public Policy Board. In the coming days and weeks the Task Force will provide a detailed explanation of the proposed rule to help members understand how CMS’ proposals may affect nephrology care. Please visit ASN’s ESRD bundling webpage to get the latest information on the QIP at http://asn-online.org/policy_and_public_affairs/esrd-bundling.aspx.

Atoarvastatin Beats Rosuvastatin in Protecting Kidneys in Diabetic and Nondiabetic Patients

Two related trials investigating the effects of statins on urinary protein excretion and kidney function found atorvastatin (ATV) protective and rosuvastatin (RSV) nonprotective or possibly harmful in diabetic or nondiabetic patients. High-dose ATV significantly reduced proteinuria and did not affect renal function. RSV, on the other hand, was associated with a significant decline in function and had no effect on proteinuria.

In diabetic and nondiabetic patients, proteinuria is a risk factor for further loss of kidney function and progression to end stage renal disease, even when ACE inhibitors or angiotensin receptor blockers (ARBs) are used to lower blood pressure. Experimental results have suggested that the use of statins may reduce proteinuria and preserve kidney function.

At the XLVII European Renal Association-European Dialysis and Transplantation Association conference, Dick De Zeeuw, MD, PhD, a clinical pharmacologist at the University Medical Center in Groningen, The Netherlands, reported on the PLANET trials. These randomized, double blind, multinational trials tested the effects of ATV 80 mg/day or RSV 10 mg/day or 40 mg/day on urinary protein

excretion and renal function in hypercholesterolemic patients with moderate proteinuria.

PLANET I enrolled 325 patients with type 1 or 2 diabetes, and PLANET II involved 220 patients without diabetes. Patients had urinary protein/creatinine ratios of 500–5000 mg/g and fasting LDL cholesterol ≥ 90 mg/dL. They had used ACE inhibitors or ARBs for at least three months prior to screening.

After an eight-week lead-in period, patients were put on drug. The patients randomized to receive RSV 40 mg/day or ATV 80 mg/day took half the daily dose for the first four weeks and then escalated to full doses. Patients with severe renal disease, defined as an estimated glomerular filtration rate (eGFR) of <40 mL/min/1.73 m², or in PLANET I with a hemoglobin A1c >11 percent, were excluded from the study, as were people with active liver disease.

The primary endpoint of the studies was the change in urinary protein/creatinine ratio from baseline to week 52 or to the last on-treatment observation carried forward. The patients in the three treatment arms were fairly well matched within each trial for their baseline characteristics, including mean eGFRs, mean protein/creatinine ratio, and mean albumin/creati-

nine ratio.

For PLANET I, De Zeeuw said, “Atorvastatin significantly reduces the proteinuria in these patients on top of ACE/ARB therapy with around 15 percent reduction in proteinuria, whereas with rosuvastatin both 10 and 40 mg had no significant effect at all on proteinuria.” The effect of ATV was evident by week 26.

In PLANET II, “we see a similar pattern, even more pronounced,” he said. ATV reduced proteinuria by >20 percent at 26 and 52 weeks, but there was no significant effect with either dose of RSV.

For eGFR, De Zeeuw said the results were “very surprising” in that the PLANET I patients on RSV lost more kidney function over 52 weeks than did the ATV group. Patients on ATV lost about 1–2 mL/min/1.73 m² over 52 weeks, the group on RSV 10 mg/day lost about 4 mL/min/1.73 m², and the RSV 40 mg/day group lost close to 8 mL/min/1.73 m².

In nondiabetic patients (PLANET II) the effects of the treatments on kidney function were slightly less pronounced. There was a significant decline in eGFR with RSV 40 mg/day but not in the other two treatment arms.

All the treatments lowered total and

LDL cholesterol to about the same degree, and all were well tolerated in both trials.

He concluded from these findings that in diabetic or nondiabetic patients with proteinuria, using optimal therapy, including ACE inhibitors and ARBs:

- ATV 80 mg/day significantly reduced proteinuria by about 20 percent
- RSV 10 or 40 mg/day had no effect on proteinuria
- RSV 40 mg/day was associated with a significant decline in eGFR of about 8 mL/min/1.73 m²/year
- ATV 80 mg/day had no effect on eGFR
- ATV 80 mg/day had a clear advantage over RSV 40 mg/day in terms of renal protection or renal damage

Multiple clinical trials have led clinicians to view most statins as fairly similar, a so-called “class effect” for this class of drugs. De Zeeuw said this trial “sort of dismembers the class effect,” at least for the parameters studied here. “I think this ‘class’ discussion is going to be extremely important,” he added, and advised, “If you are considering putting such a patient on a statin, you should not put them on rosuvastatin.” ●

Allopurinol Reduces Left Ventricular Hypertrophy in CKD

High-dose allopurinol treatment caused regression of left ventricular hypertrophy (LVH) and improvement of endothelial function in patients with stage 3 chronic kidney disease (CKD). Allopurinol is an inhibitor of the enzyme xanthine oxidase and acts as an anti-oxidant by preventing the formation of free radicals from the action of the enzyme.

Patients with even mild to moderate kidney disease are at greatly elevated risk of cardiac morbidity and mortality, including LVH, said Michelle Kao, MBChB, a clinical research fellow at the University of Dundee, UK, “Increasingly, people are beginning to appreciate that oxidative stress plays a major part in this poor overall outcome in patients with advanced renal disease,” she said.

She told an audience at the European Renal Association-European Dialysis and Transplantation Association congress that studies have indicated that oxidative stress manifests as LVH and endothelial dysfunction. LVH is a strong cardiac risk factor because it is arrhythmogenic and reduces coronary perfusion reserve, leading to diastolic heart failure and to left atrial dilatation, a precursor of atrial fibrillation and embolic stroke.

Xanthine oxidase as a target

One source of oxidative stress is the purine degradation pathway, in which xanthine oxidase converts hypoxanthine to xanthine, with the release of free radical byproducts, leading to oxidative stress. Thus, inhibiting xanthine oxidase should block the generation of some free radicals. Kao reported that xanthine oxidase inhibition has been shown to improve endothelial function in diabetics, smokers, hypercholesterolemic patients, and those with congestive heart failure. But it has never been investigated in patients with CKD.

So she tested the effect of high-dose allopurinol on endothelial function and LVH in patients with CKD. Using cardiac magnetic resonance imaging, she measured left ventricular mass (LVM) at baseline and at nine months in a randomized, double-blind, placebo-controlled trial. LVH was determined by echocardiography. Endothelial function was determined by ultrasound measurement of flow-mediated dilatation (FMD) of the brachial artery after release of artery occlusion with a cuff. The degree of reactive dilatation is an indication of arterial stiffness.

Stage 3 CKD patients were randomly assigned to an allopurinol arm (n = 27) or to a placebo arm (n = 26). The allopurinol group received the drug at 100 mg/day for two weeks, which was increased to 300 mg/day if it was well tolerated and did not adversely affect kidney function. All baseline characteristics were similar between the two groups except that the allopurinol arm had a slightly lower diastolic blood pressure (70 ± 8 mm Hg vs. 75 ± 8 mm Hg). Patients were well matched for LVM, and most were already on an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker.

“We found that those patients on allopurinol had regression of the LV [left ventricular] mass after nine months [-1.42 ± 4.67 g/m²] compared to progression for those patients in the placebo group [$+1.28 \pm 4.45$ g/m²],” Kao reported. “We also found a trend toward improvement in end-diastolic volume for those patients on allopurinol.”

Endothelial function, as indicated by FMD, improved for the allopurinol group. “This suggests to us that perhaps some of the beneficial effects seen on the LV mass index were due to an improvement in the vascular

compliance and the LV afterload,” she said.

There were no differences between the two arms of the trial in terms of blood pressure, renal function, or the prevalence of adverse events. Serum uric acid levels were lower in the allopurinol group (but did not correlate with the changes in LVM index seen).

“We found for the first time that allopurinol can regress LVH in man. And we also found that allopurinol can improve both endothelial dysfunction and arterial stiffness in patients with CKD,” Kao concluded. She said yet to be tested is whether these effects translate into improvements in hard clinical endpoints, such as cardiac events or death. She has blood samples and will test them for markers of oxidative stress to confirm whether the changes seen correlate with the level of oxidative stress.

David Harris, MD, of the University of Sydney in Australia, commented that if this study is confirmed by larger ones, it could change clinical practice “because it’s the first trial that’s shown a reduction in left ventricular mass with allopurinol, [and] I think that’s a very important outcome.” ●

Adynamic Bone Disease Raises Risk of Vascular Calcification

By Daniel Keller

The field of adynamic bone disease has moved quickly in the past decade from consideration of the kidney-bone axis, with concern about renal osteodystrophies and the impact of kidney disease on bone, to a concept of chronic kidney disease (CKD) and its relation to mineral and bone disorders (CKD-MBD). The latter is a broader clinical syndrome encompassing not only bone abnormalities but also laboratory abnormalities and vascular calcification and has been associated with increased mortality in the dialysis population.

Characterized by reduced bone turnover, adynamic bone disease is increasingly recognized as the most common form of renal osteodystrophy. Adynamic bone disease is particularly common in peritoneal dialysis populations. Constant exposure to calcium in dialysate fluids leads to episodic hypercalcemia, suppression of parathyroid levels, and therefore, adynamic bone. The bone has normal mineralization and low or normal bone volume but few or no osteoblasts or osteoclasts.

Jordi Bover, MD, PhD, of the nephrology department at Fundació Puigvert in Barcelona, Spain, spoke at the XLVII European Renal Association-European Dialysis and Transplantation Association conference, about the “bone-vascular axis” in adynamic bone disease. “During the last decades...we have observed an increased prevalence of adynamic bone

disease,” he said. Among the reasons are increased awareness and diagnosis, more dialysis of elderly and diabetic patients, high calcium load from dialysis solutions, vitamin D overtreatment, patients on peritoneal dialysis being at slightly more risk, the presence of malnutrition-inflammation syndrome, hypogonadism, and treatment with bisphosphonates.

Finally, low levels of parathyroid hormone (PTH) or bone resistance to PTH can lead to adynamic bone disease. “Skeletal resistance to the action of PTH has been known for many, many years,” Bover said and compared it to resistance to several other hormones, such as insulin and growth hormone in the uremic state.

Although bone biopsy is the definitive method to diagnose adynamic bone disease, other less invasive approaches can also be used. However, none of the biochemical markers has reached a sufficient level of diagnostic accuracy. Bover said low serum levels of intact PTH (iPTH, <100 pg/mL) are associated with adynamic bone disease. High levels of bone alkaline phosphatase “virtually exclude adynamic bone disease,” he told the audience.

Risk of vascular calcification

A diagnosis of adynamic bone disease is important since patients with the

disease have more bone pain, and the risk of fractures is increased, probably because the bone has a diminished capacity to repair microdamage. “The most important association of adynamic bone disease is the presence of arterial or coronary calcifications or the association with calcemic uremic arteriopathy, such as calciphylaxis,” Bover said. Calciphylaxis is a syndrome of vascular calcification, thrombosis, and skin necrosis.

Abnormal calcium balance makes it hard for the body to incorporate calcium into bone, and the highest aortic calcification scores have been associated with low bone turnover. Similarly, low bone turnover has been shown to increase coronary artery calcification and progression. “This is one of the reasons we are trying to underline the importance of this “neo” bone-vascular axis,” Bover emphasized.

He showed data indicating that patients with high or low levels of iPTH are at increased risk of death. The lowest mortality risk occurred when iPTH, calcium, and phosphate levels were within the KDOQI (Kidney Disease Outcomes Quality Initiative) ranges.

Although the management of adynamic bone disease has not been investigated well and randomized trials are absent, adynamic bone disease is

reversible in a substantial number of patients. Bover recommended:

- stopping aluminum exposure and initiating chelation treatment (deferoxamine)
- reducing the calcium load
- reducing vitamin D overload
- restoring PTH activity with the new pharmacologic compounds
- changing from calcium-containing phosphate binders to sevelamer or lanthanum
- decreasing the calcium content in dialysate for patients with diagnosed adynamic bone disease

Bover concluded that adynamic bone disease is increasingly found in patients with CKD and is associated with an increased risk of vascular calcification. There is a need for better noninvasive biomarkers of bone activity as well as of risk for cardiovascular calcification. He said nephrologists need to be aware of the PTH assay kit they are using to be able to keep patients in the optimal range. Normal PTH levels are probably not desirable in nondialysis or dialysis CKD patients. Although many patients in the KDOQI-recommended range also suffer from ADB, these patients are the ones with the highest survival, Bover said. ●

Restless Legs Syndrome More Prevalent Among Hemodialysis Patients, Correlates With CRP Levels

By Daniel Keller

Restless legs syndrome (RLS) affects patients on chronic hemodialysis about four times as often as it does the general population. An Italian research team showed an association of RLS with blood levels of C-reactive protein (CRP) in chronic hemodialysis patients at the European Renal Association-European Dialysis and Transplant Association Congress.

RLS interferes with sleep by causing patients an urge to move the legs when at rest. Patients may complain of insufficient and non-restorative sleep and of daytime sleepiness and diminished functioning. People with RLS also have a higher prevalence of anxiety and depression.

The “primary” form of RLS affects about 5 percent of the general population and does not appear to have an underlying cause. Another form is secondary to other medical conditions or treatments, such as hemodialysis.

From a study of 58 chronic hemodialysis patients, lead investigator Giulio Romano,

MD, professor of nephrology at the University of Udine and S.M. Misericordia University Hospital in Udine, Italy, found a prevalence of RLS of 21.4 percent. RLS patients were defined as those who experienced symptoms at least twice a week.

The 12 patients with RLS in this study took much longer to fall asleep, slept less at night, took longer naps, and had more insomnia and daytime sleepiness compared with 46 hemodialysis patients without RLS.

Among RLS patients on chronic hemodialysis, “the interesting conclusion of our work is that there is a correlation between restless legs syndrome and an increase of inflammatory cytokines and the increase of CRP,” Romano said. The total sleep time correlated negatively with the level of serum CRP. The higher the CRP, the shorter the sleep time was. The group of patients with RLS had a serum CRP level of 43.96 ± 23.71 mg/L versus 15.24 ± 3.94 mg/L for the non-RLS patients ($p = 0.04$). Even in

the chronic hemodialysis patients without RLS, CRP levels were about three times the upper limit of normal in the general public, Romano said.

Looking at a variety of other common laboratory parameters, the researchers found a significant difference between patients with or without RLS only for serum iron and for percent transferrin saturation. There were no significant differences between the groups in regard to hemoglobin, hematocrit, urea, creatinine, albumin, or parathyroid hormone levels, nor to Kt/V, indicating that under-dialysis was not the cause of the RLS.

Several studies have shown that increased inflammation is associated with elevated cardiovascular risk in patients on chronic hemodialysis, Romano said. There is also evidence that sleep disorders induce elevated levels of proinflammatory cytokines.

“We think that if patients have some sleep disorders, they evoke inflammation,” he said, “and so if we treat the sleep disor-

ders, we reduce a cardiovascular risk factor because CRP is a possible cause of increased cardiovascular risk.” Besides CRP levels, the levels of transferrin saturation, another marker of inflammation, were different between patients with or without RLS.

Antiparkinson drugs have been used to relieve RLS. So the next step, according to Romano, is to work with his colleagues in the neurology department to treat the RLS patients with such drugs to see if reducing nighttime leg movements and restoring sleep lowers CRP levels, and eventually, cardiovascular risk.

Although cardiovascular events (e.g., nonfatal and fatal heart attacks) are associated with elevated levels of CRP and are the main cause of death among hemodialysis patients, it would make sense to look at other markers of inflammation as well. “We have to find out all risk factors,” said Nageswara Reddy, MD, assistant professor of nephrology at Manipal University in India. ●

Journal View

No Clear Benefit of mTOR Inhibitors for ADPKD

Everolimus and sirolimus do not appear effective in the treatment of autosomal dominant polycystic kidney disease (ADPKD), according to a pair of clinical trials presented at the 70th Scientific Sessions of the American Diabetes Association and published by *The New England Journal of Medicine*.

The trials evaluated the effects of the two mammalian targets of rapamycin (mTOR) inhibitors on relevant clinical outcomes in patients with ADPKD. In the larger of the two trials, 433 patients with ADPKD and stage 2 or 3 chronic kidney disease were randomly assigned to two years of treatment with everolimus or placebo. All patients had an average baseline renal volume greater than 1500 mL.

Everolimus was associated with a smaller increase in total kidney volume: 203 mL at two years, compared to 301 mL in the placebo group. Yet there was no associated improvement in kidney function—mean decrease in estimated glomerular filtration rate was 8.9 and 7.7 mL/min/1.73 m², respectively. Patients in the everolimus group had more drug-specific adverse events.

In the other trial, 100 patients with

early-stage ADPKD—average total kidney volume approximately 1000 mL—were randomly assigned to sirolimus or standard care. At 18 months, the median increase in total kidney volume was about 100 percent in both groups. There was also no significant difference in glomerular filtration rate, but the sirolimus group had a higher urinary albumin excretion rate.

The results are disappointing in light of promising experimental and observational studies. An accompanying editorial discusses the implications for future studies, highlighting the urgent need for “better tools for assessing the effects of our interventions on renal function in humans.” [Walz G, et al. Everolimus in patients with autosomal dominant polycystic kidney disease. Published at www.nejm.org June 26, 2010 (10.1056/NEJMoa1003491); Serra AL, et al: Sirolimus and kidney growth in autosomal dominant polycystic kidney disease. (10.1056/NEJMoa09074190); Watnick T, Germino GG: mTOR Inhibitors in Polycystic Kidney Disease. (10.1056/NEJMe1006925)]. ●

FGF23 Affects Bone Metabolism in Pediatric CKD

Fibroblast growth factor 23 (FGF23)—a predictor of cardiovascular complications of chronic kidney disease (CKD) in adults—has an important impact on bone metabolism in children with CKD, reports a study in *Kidney International*.

The cross-sectional study included 69 children with CKD of various causes, representing all stages of renal dysfunction. Levels of FGF23 and other biochemical variables of bone metabolism were assessed.

Mean FGF23 level increased from 47 ng/L in children with stage 1–2 CKD, to 144 ng/L for those in stage 3, 313 ng/L in stage 4, and 734 ng/L in stage 5. Thus significant elevation of FGF23 was already present before the development of hyperphosphatemia in stage 4 CKD.

The increases in FGF23 were positively correlated with parathyroid hormone and phosphate levels and negatively correlated with 1,25-dihydroxyvitamin D, estimated glomerular filtration rate, and tubular phosphate reabsorption. On multivariate analysis, hyperphosphatemia and

low estimated glomerular filtration rate were the factors most strongly related to FGF23.

Fibroblast growth factor 23, which regulates renal phosphate reabsorption, is increased in adults with CKD, in whom it has been linked to cardiovascular morbidity. There are very few data on the levels and effects of FGF23 in pediatric CKD.

The new results show that, in children as in adults with CKD, FGF23 levels increase gradually with disease stage. Even at an early stage of CKD in children, FGF23 appears to have an important impact on calcium and phosphate homeostasis and vitamin D metabolism. “FGF23 is a novel and important biomarker in children with chronic renal failure,” the investigators conclude. They call for further studies of its effect on bone disease, growth failure, and cardiovascular morbidity [van Husen M, et al: Fibroblast growth factor 23 and bone metabolism in children with chronic kidney disease. *Kidney Int* 2010; 78:200–206]. ●

Monitoring Avoids Hyperkalemia from Spironolactone

With attention to serum potassium and creatinine levels, increased use of spironolactone for heart failure does not lead to a higher rate of hospital admissions for hyperkalemia, according to a study in the *British Medical Journal*.

National Health Service records for Tayside, Scotland, were reviewed to track trends in prescribing of spironolactone and hospitalizations for hyperkalemia from 1994 to 2007. The goal was to assess the impact of the 1999 Randomized Aldactone Evaluation Study (RALES), which found that spironolactone improves outcomes in severe heart failure.

Prescriptions for spironolactone rose sharply after the publication of RALES: from about 2800 prescriptions in the first half of 1999 to 6600 in the second half of 2001. There were significant and parallel increases in the number of serum creatinine and potassium measurements performed. These trends were not limited to patients with heart failure. Hospital admissions for hyperkalemia remained very low throughout the study period.

Among patients with recent hospi-

talization for heart failure who were receiving an angiotensin-converting enzyme inhibitor, the rate of spironolactone use increased from 19.8 per 100 patients in early 1999, to 70.1 per 100 patients in late 2001, to 61.3 per 100 patients in 2007. At the same time, the rate of outpatient potassium measurements showing hyperkalemia (serum potassium level over 6 mmol/L) decreased from 9.9, to 6.9, to 2.9, respectively, per 100 patients.

Previous reports linked the increased use of spironolactone in response to RALES to an increased rate of severe hyperkalemia. But the experience in Tayside suggests that with increased serum potassium and creatinine monitoring, hospitalizations for hyperkalemia remain low—despite increased spironolactone prescribing. The researchers write, “Spironolactone prescribing seems to be safe in the setting of the NHS, probably owing to careful monitoring of electrolytes and renal function.” [Wei L, et al. Spironolactone use and renal toxicity: population based longitudinal analysis. *BMJ* 2010; 340:c1768]. ●

TMP-SMX Linked to Hyperkalemia in Elderly—With or Without β -Blockers

The increased risk of hyperkalemia in older adults taking trimethoprim-sulfamethoxazole (TMP-SMX) is unrelated to concomitant β -blocker treatment, according to a study in the *Clinical Journal of the American Society of Nephrology*.

Linked Ontario health data were used to assess the relationship between TMP-SMX use and hospital admission for hyperkalemia among older adults taking β -blockers. The analysis included nearly 300,000 patients, aged 66 years or older, receiving β -blockers between 1994 and 2008. In this cohort, 189 patients were hospitalized within 14 days after receiving a prescription for antibiotics commonly used for the treatment of urinary tract infections: TMP-SMX, amoxicillin, ciprofloxacin, norfloxacin, or nitrofurantoin.

Of case patients admitted for hyperkalemia, 51.9 percent were taking TMP-SMX, compared to 19.5 percent of matched controls without hyperkalemia. On adjusted analysis, TMP-SMX was associated with a fivefold increase in the risk of hospitalization for hyperkalemia compared to amoxicillin. None of the other antibiotics was

related to hyperkalemia risk.

Analysis of a cohort of non- β -blocker users included 1349 hyperkalemia cases and 5378 controls. The results showed a similar increase in hyperkalemia requiring hospital admission among TMP-SMX users.

The TMP-SMX combination, one of the most widely prescribed antibiotics in North America, decreases the kidney's ability to eliminate potassium. It has been suggested that simultaneous use of TMP-SMX and β -blockers may confer a high risk of hyperkalemia.

The new results confirm the increased risk of hospitalization for hyperkalemia in older adults taking TMP-SMX, regardless of concomitant β -blocker therapy. Measuring blood potassium in patients prescribed TMP-SMX could potentially decrease the risk of hyperkalemia associated with TMP-SMX, the authors suggest [Weir MA, et al. Beta-blockers, trimethoprim-sulfamethoxazole, and the risk of hyperkalemia requiring hospitalization in the elderly: a nested case-control study. *Clin J Am Soc Nephrol* 2010 doi: 10.2215/CJN.01970310]. ●

Letters

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CARE-2 Study

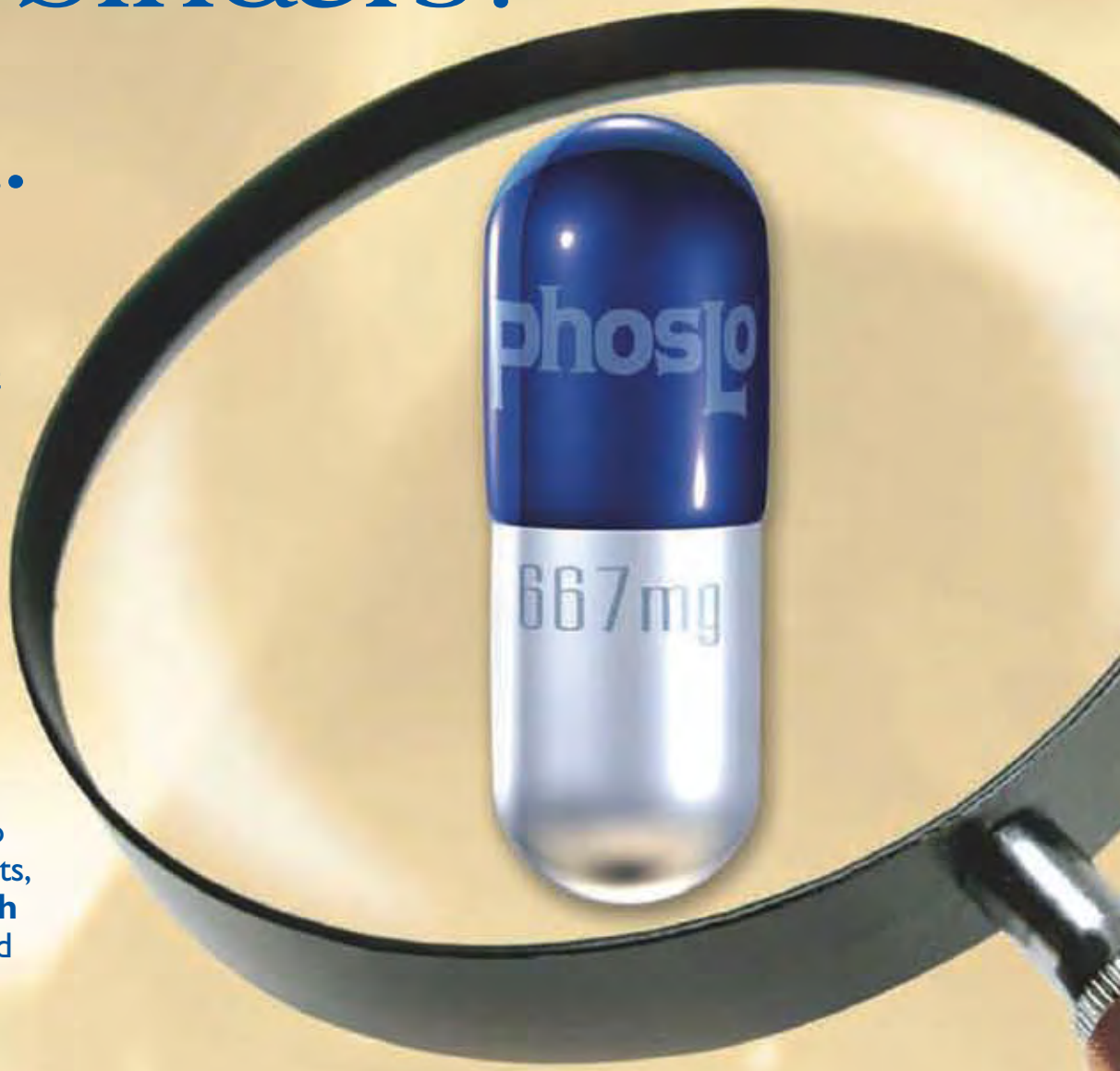
- The CARE-2 study demonstrated **NO significant difference in the progression of coronary artery calcification** following equivalent lipid control in the PhosLo and sevelamer treated groups.²

DCOR Study

- DCOR, a Genzyme-sponsored study, failed to achieve both primary and secondary endpoints, demonstrating **NO mortality benefits with sevelamer** when compared to calcium-based phosphate binders.³

DOPPS II Study

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- PhosLo has not been associated with metabolic acidosis.⁶
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PhosLo® is indicated for control of hyperphosphatemia in end-stage renal failure. Patients with higher-than-normal serum calcium levels should be closely monitored and their dose adjusted or terminated to bring levels to normal. **PhosLo® is contraindicated in patients with hypercalcemia.** No other calcium supplements should be given concurrently with PhosLo.® Nausea, hypercalcemia and pruritus have been reported during PhosLo® therapy.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

CONTRAINDICATIONS: Patients with hypercalcemia. **INDICATIONS AND USAGE:** For the control of hyperphosphatemia in end-stage renal failure. **WARNINGS:** Patients with end-stage renal failure may develop hypercalcemia when given calcium with meals. No other calcium supplements should be given concurrently with PhosLo. Progressive hypercalcemia due to overdose of PhosLo may be severe as to require emergency measures. Chronic hypercalcemia may lead to vascular calcification, and other soft-tissue calcification. The serum calcium level should be monitored twice weekly during the early dose adjustment period. The serum calcium times phosphate ($\text{Ca} \times \text{P}$) product should not be allowed to exceed 66. Radiographic evaluation of suspect anatomical region may be helpful in early detection of soft-tissue calcification. **PRECAUTIONS:** Excessive dosage induces hypercalcemia; therefore, early in the treatment during dosage adjustment serum calcium should be determined twice weekly. Should hypercalcemia develop, the dosage should be reduced or the treatment discontinued immediately depending on the severity of hypercalcemia. Do not give to patients on digitalis, because hypercalcemia may precipitate cardiac arrhythmias. Always start PhosLo at low dose and do not increase without careful monitoring of serum calcium. An estimate of daily calcium intake should be made initially and the intake adjusted as needed. Serum phosphorus should also be determined periodically. **Information for the Patient:** Inform the patient about: 1) compliance with dosage, 2) adherence to diet instructions and avoidance of nonprescription antacids, and 3) symptoms of hypercalcemia. **Drug Interactions:** PhosLo may decrease the bioavailability of tetracyclines. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term animal studies have not been performed. **Pregnancy:** Teratogenic Effects: Category C. Animal reproduction studies have not been conducted. It is not known whether PhosLo can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Give to a pregnant woman only if clearly needed. **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use:** Of the total number of subjects in clinical studies of PhosLo ($n = 91$), 25 percent were 65 and over; while 7 percent were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **ADVERSE REACTIONS:** In clinical studies, patients have occasionally experienced nausea during PhosLo therapy. Hypercalcemia may occur during treatment with PhosLo. Mild hypercalcemia ($\text{Ca} > 10.5 \text{ mg/dl}$) may be asymptomatic or manifest itself as constipation, anorexia, nausea and vomiting. More severe hypercalcemia ($\text{Ca} > 12 \text{ mg/dl}$) is associated with confusion, delirium, stupor and coma. Mild hypercalcemia is easily controlled by reducing the PhosLo dose or temporarily discontinuing therapy. Severe hypercalcemia can be treated by acute hemodialysis and discontinuing PhosLo therapy. Decreasing dialysate calcium concentration could reduce the incidence and severity of PhosLo induced hypercalcemia. The long-term effect of PhosLo on the progression of vascular or soft-tissue calcification has not been determined. Isolated cases of pruritus have been reported which may represent allergic reactions. **OVERDOSAGE:** Administration of PhosLo in excess of appropriate daily dosage can cause severe hypercalcemia (see ADVERSE REACTIONS).

For more information on PhosLo®, please contact Fresenius Medical Care at 800-323-5188.

Manufactured for and distributed by: Fresenius Medical Care North America, Waltham, MA 02451



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1. Qunibi WY, Hootkins RE, McDowell LL, et al. Treatment of hyperphosphatemia in hemodialysis patients: The calcium acetate renagel evaluation (CARE Study). *Kidney International* 65:1914-1926, 2004. 2. Qunibi WY, Moustafa M, Kessler P, et al. Coronary artery calcification in hemodialysis patients: Preliminary results from the calcium acetate renagel evaluation-2 (CARE-2) study. Poster session presented at the International Society of Nephrology/World Congress of Nephrology Meeting in Rio de Janeiro, Brazil: April 21-25, 2007. 3. Suki VVN, Zabaneh R, Cangiano JL, et al. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. *Kidney International* Aug 29, 2007. 4. Young EW, Albert JM, Akizawa T, et al. Sevelamer vs. calcium-containing phosphate binders and mortality in the dialysis outcomes and practice patterns study (DOPPS). *J Am Soc Neph* 16:Abstract, 2005. American Society of Nephrology. Renal Week. Pennsylvania Convention Center, Philadelphia, PA, November 8-13, 2005. 5. PhosLo [prescribing information]. Fresenius Medical Care, Waltham, MA; January 2007. 6. Mehrotra R, Kopple JD, Wolfson M. Metabolic acidosis in maintenance dialysis patients: clinical considerations. *Kidney International* 64(suppl 88):S13-S25, 2003. 7. Drug Topics Redbook (Montvale, NJ: Thomson Healthcare), 2007.

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Industry Spotlight

GlaxoSmithKline's Avandia Found to Increase Heart Disease and Stroke

The type 2 diabetes drug Avandia (rosiglitazone; manufactured by GlaxoSmithKline [GSK]) is in the news again. Two separate and dissimilar studies found Avandia increased the risk of heart attack and other conditions.

These studies set the stage for a public debate within the U.S. Food and Drug Administration (FDA) advisory panel, which convened to discuss the safety of Avandia in July. After hearing the evidence and many presentations, most of the 33 panel members recommended the continued sale of Avandia with new usage restrictions or warnings on the drug's labeling. Twelve panel members said the drug should be fully withdrawn.

The panel's general conclusion was that although Avandia does increase the chance of a heart attack, its chances of increasing the risk of mortality are very small. According to the *Boston Herald*, most panel members felt it was important to keep Avandia on the market as an alternative to Actos (pioglitazone; manufactured by Takeda Pharmaceuticals, Osaka, Japan), another drug for type 2 diabetes, because not everyone will have an effective course of treatment with Actos.

The European Medicines Agency will conduct a review of Avandia in a manner similar to that of the FDA's review. The agency could then revoke or change marketing authorization for the drug in Europe.

One of the American studies was published in the *Journal of the American Medical Association* by David Graham, a drug safety researcher at the U.S. Food and Drug Administration (FDA). Graham and his colleagues analyzed insurance records of 227,571 patients who took either Avandia or Actos and found that Avandia increased both the risk for heart attack and stroke. Avandia patients were 27 percent more likely to have a stroke, 25 percent more likely to develop heart failure, and 14 percent more likely to die. There was an 18 percent increased risk for all three outcomes, in addition to heart attack.

The other study, by outspoken and long-time Avandia opponent Steve Nissen of the Cleveland Clinic, found a 39 percent higher chance of heart attack in patients who used Avandia. Nissen's results were published in the *Archives of Internal Medicine* in an updated study on Avandia; in 2007, Nissen and his research team found and reported a similar increased risk of

heart attacks and heart failure in patients who used the drug.

Avandia can present several challenges, including heart-related adverse events such as fluid retention and congestive heart failure. The drug is monitored per FDA directives for these and other events.

Overall, shares of GSK have fallen 13 percent in the past year, according to *Bloomberg Businessweek*. To date, more than 4000 lawsuits have been filed against GSK because of Avandia's effects on the heart and circulatory system. In May, the company agreed to pay \$60 million in the first settlements of the litigation, according to sources familiar with the agreement, *Bloomberg Businessweek* reported.

Avandia's use fell sharply after Nissen's first study, but the medicine is still widely prescribed, with sales of \$1.2 billion in 2009, Reuters reported. It loses patent protection in 2012.

The Graham study convinced epidemiologist Corinne de Vries of the University of Bath, United Kingdom, of the drug's problems. "I can't fault it, and I suspect it might be the nail in the coffin for rosiglitazone," she said in a news report for the journal *Nature*. ●



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Fellows Corner

How to Formulate a Research Question

By Nathan Hellmann

All renal fellows are required to perform some type of research during the course of their training. For some, this research will be a stepping stone to a career in academic nephrology. For others, the research years will be a brief sojourn into a different realm for a year or two, until private practice beckons. Out of the myriad options available, how does one choose a worthy research question?

Choosing a research mentor is intimately linked to choosing a research question. Except for the few brave souls who are already independently minded (and independently funded) coming into fellowship, nephrology fellows will need to find a mentor, someone who will not only help develop the research question into a full-fledged independent project, but also provide career advice and allow fellows to build upon previous discoveries and techniques developed by the lab.

Finding the right mentor and the right project can be a challenge, particularly when nephrology fellows are required to commit to a specific laboratory very early on, usually during the notoriously difficult clinical year during which free time can be hard to come by. Fellows are typically asked to commit to a given “track”—basic science, clinical research, and clinician-educator are common choices—that allows fellowship programs to plan for the future and ensure a healthy balance of research and clinical fellows.

“I think in general you need to choose the best combination of mentor and project that fits with your individual needs,” said Jonathan Bazeley, MD, a recent graduate of the University of Michigan nephrology fellowship program. “Something which really helped [in our nephrology fellowship program] was that renal fellows have a protected two-week block of time halfway through the clinical fellowship intended for fellows to go around and interview with the faculty of the nephrology division to discuss potential projects.”

Not all nephrology fellowship programs have such blocks, so most would agree that fellows will need to set aside some time to discuss possible experimental ideas with poten-

tial mentors in anticipation of the upcoming research years. Talking directly with current and former fellows about a given mentor can also be invaluable in identifying potential conflicts or mismatches before they occur.

Although some fellows may feel uncomfortable making such decisions so early on in their fellowship, a case can be made that it justly forces fellows to ask themselves essential questions about where they see their career evolving. The choice of mentor may be very different depending on whether or not an individual wants to stay within academics or begin their clinical practice career.

A large, 30-plus person laboratory studying mechanisms of transplant immunobiology may not be the best fit for an individual without much research experience who simply wants to develop a clinical practice after completing fellowship. Large labs tend to favor individuals with an ability to carry out a project independently. This is not to say that fellows who do not anticipate staying within research should automatically rule out the possibility of trying a basic science lab. In the right scenario with good one-on-one mentoring, a rewarding research experience can be achieved.

For individuals who think they want to have a career predominantly in research, the decision as to which mentor and research question to choose are even more critical. Should one choose the department head who has 258 publications to his name, access to exciting scientific reagents or databases, but will only be able to meet individually with fellows once every three months? Or should one choose the up-and-coming junior faculty member who is able to provide lots of individual attention and quality mentoring but may be unable to provide guaranteed funding for the duration of the project? Ultimately, the decision comes down to the individual, but most would agree that a good rapport with the mentor should exist prior to joining the lab.

Narrowing down the focus

Key to a good research question is how to narrow down the focus to a question specific enough to obtain meaningful conclusions, but glo-

bally interesting to the field of nephrology. Someone who hopes to stay in research may choose to tackle an ambitious, long-term project—think something along the lines of “developing an animal model to determine the permeability factor responsible for FSGS,” for example. Someone who prefers to restrict his or her time in the lab to only one to two years and a guaranteed publication or two might decide instead to mine existing patient databases for factors that predispose toward CKD in a specific patient subpopulation. Regardless of the scope, asking the following questions can be useful in honing in on a research focus:

1. Is the question I’m asking important? Even for basic science types, in the current funding climate it is often necessary to justify a project based on its relevance to human disease.
2. Is the project doable in the allotted amount of time? More ambitious, long-term projects should be embarked on only by those with the stomach for a long-term research career. Knowing what tools are available to you is essential for answering this question.
3. Is my research question specific enough? Generally speaking, the more specific, the better. It’s not enough to say, “I want to study dialysis access.” Instead, ask a directed question such as, “I want to study the incidence/prevalence rates of AV fistula use in this subpopulation of the ESRD population using this particular database and using these particular statistical techniques.”
4. Will I be funded? Many nephrology programs have a training grant that can guarantee fellow funding for research. However, not all fellows (particularly those from abroad) are eligible for these grants. Many programs strongly encourage individuals to apply for their own funds. It’s much better to know about these policies ahead of time.

Finally, it’s important to realize that nothing is set in stone. The research question a fellow investigates can evolve dramatically. John Forman,



MD, a nephrologist at Brigham and Women’s Hospital who has published several important papers regarding the epidemiology of hypertension, started his fellowship research in a basic research lab before switching to a clinical research pathway after a full year of research.

“I found that at the end of the day, I would be much more interested in talking about clinical research questions than basic research questions, and I realized that I could be very happy pursuing a career in clinical research,” Forman said.

Having to change one’s research focus is not altogether uncommon, especially in light of the difficulties of grant writing or experimental planning during the clinical year. In terms of formulating an appropriate research question, Forman noted the importance of having the fellow choose the actual question with guidance from the mentor, rather than simply being handed a research project. “You’ve got to pick something that you can do in a relatively short period of time with the resources available to you,” he said.

Although formulating the research question may seem intimidating to the early nephrology fellow, many find it among the most useful lessons of fellowship and see the process as an essential part of their education. ●

Renal fellow Nathan Hellman, MD, passed away February 13, 2010. Hellman had been a member of the ASN Kidney News editorial board.

ASN News

Society Announces Grant Recipients

ASN is pleased to announce grant recipients for 2010.

The following three grants provide funding for young faculty to foster evolution to an independent research career by providing transition funding toward successful application for an R01 grant. Applicants must be within seven years of initial faculty appointment and may be in the last two years of a mentored award. Applicants must be able to show evidence of progress toward capability to oversee an independent research project or its equivalent.

Carl Gottschalk Research Scholar Recipients

Vivek Bhalla, MD, FASN
Stanford University School of Medicine

David M. Charytan, MD
Brigham and Women's Hospital

Paolo Fiorina, MD, PhD
Children's Hospital Boston
Harvard Medical School

Akio Kobayashi, PhD
Brigham and Women's Hospital

Vladimir Pech, MD
Emory University School of Medicine

Timo M. Rieg, MD
University of California, San Diego School of Medicine

Simone Sanna-Cherchi, MD
Columbia University College of Physicians and Surgeons

John Merrill Grant in Transplantation Recipient

Joshua D. Mezrich, MD
University of Wisconsin School of Medicine and Public Health

Norman Siegel Research Grant Recipient

Massimo Attanasio, MD

University of Texas Southwestern Medical Center
Three recipients were named for the M. James Scherbenske Grant. The purpose of this grant is to provide bridge funding for investigators from R01 to R01 whose application was not funded. Applicants are eligible only during the period of first revision of R01.

M. James Scherbenske Grant Recipients

Melissa A. Cadnapaphornchai, MD
University of Colorado School of Medicine

Mary E. Choi, MD
Harvard Medical School, Brigham and Women's Hospital

Leonidas Tsiokas, PhD
University of Oklahoma Health Sciences Center



Student Scholar Grants enable selected medical students with an interest in either basic or clinical research to spend from 10 to 52 weeks engaged in continuous full-time research. The mentor must be an ASN member and must submit a program of study for the applicant. An award period can be a summer, semester, academic year, or any other 10- to 52-week period of continuous full-time research. Applicant must be completing research in a nephrology lab.

Student Scholar Grant Recipients

Narae Ko
Yale University School of Medicine

Dhruti Patel
Brigham and Women's Hospital

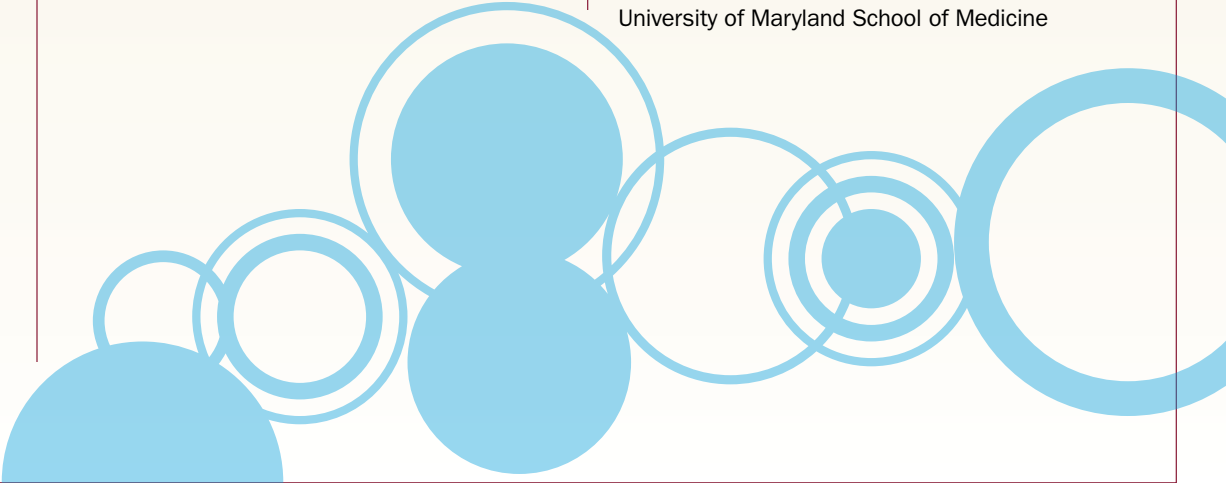
Krupa Patel
University of Maryland School of Medicine

Shannon Nees
Columbia University College of Physicians and Surgeons

Stacy Rosenberg
Tulane University School of Medicine

Ryan Reichert
Medical University of South Carolina College of Medicine

Amy Zhang
University of Maryland School of Medicine



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Policy Update

New Funds to Help Alleviate Primary Care Shortage and Expand Preventive Care Access

By Rachel Shaffer

Strengthening and expanding the primary care workforce is a pivotal component of recent health reform legislation, and the Department of Health and Human Services (HHS) recently announced a key step toward that goal: the availability of \$250 million in new workforce funding. Intended to help meet the growing demand for primary care workers, the funding—part of a new Prevention and Public Health Fund—will help train thousands of new doctors, nurses, physi-

cian assistants and other providers. Increasing access to primary and preventive care to prevent disease, improve outcomes, and shrink health care costs is a tenet of the health reform bill—but cannot be achieved without alleviating the current and growing shortage of primary caregivers. The American Association of Medical Colleges (AAMC) has estimated that if trends continue, the United States will face a deficit of approximately 21,000 primary care physicians in 2015.

Recognizing the need to reverse this trend, the first Prevention and Public Health Fund allocation funds five key initiatives—outlined below—to attract, train, and support 500 new primary care physicians (PCPs) and other providers. HHS dedicates a majority of the funds toward bolstering the ranks of primary care physicians, but also supports training of over 1000 physician extenders. For a complete funding allocation breakdown, see Table 1.

- **Establishing new nurse practitioner-led clinics:** Supporting the operation of 10 nurse-managed health clinics which assist in the training of nurse practitioners. These clinics are staffed by nurse practitioners, who provide comprehensive primary health care services to populations living in medically underserved communities.
- **Encouraging states to plan for and address health professional workforce needs:** \$5 million for states to plan and implement innovative strategies to expand their primary care workforce by 10 to 25 percent over ten years to meet increased demand for primary care services.

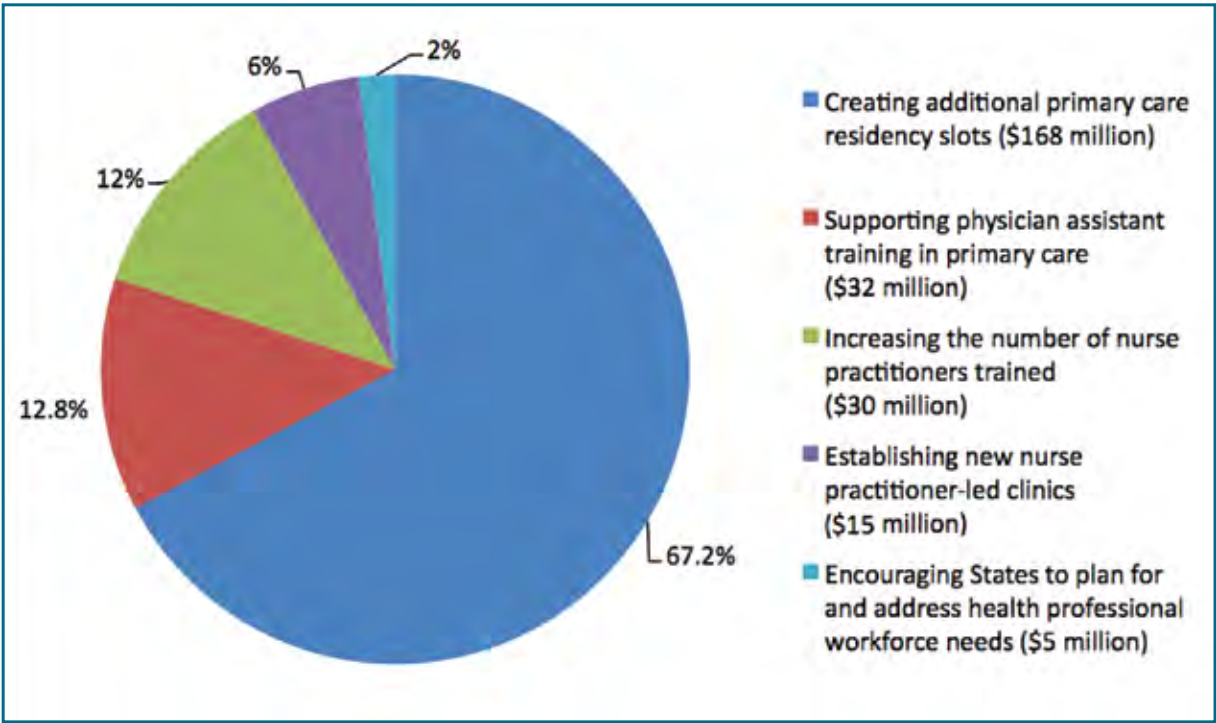
“These new investments will strengthen our primary care workforce to ensure that more Americans can get the quality care they need to stay healthy,” said HHS Secretary Kathleen Sebelius. “Primary care providers are on the front line in helping Americans stay healthy by preventing disease, treating illness, and helping to manage chronic conditions.”

While new funding will not directly add to the supply of nephrologists nationwide, it nonetheless offers benefits for patients with or at risk for kidney disease. Many people with kidney disease are unaware they have it, and as more of these individuals are able to access routine care and screenings they may be considerably more capable of preventing the progression of their condition.

“Expanding access to preventive care by growing the primary care workforce is a significant step toward earlier detection and better management of kidney disease,” said ASN Chronic Kidney Disease Advisory Group Chair Thomas DuBose, MD, FASN. “Increasing Americans’ access to routine kidney function tests and timely referrals to a nephrologist through a PCP will translate to better renal health nationwide. However, it will be even more important for us as nephrologists to work closely with the primary care community in educating these new providers about identification and care of chronic kidney disease.” ●



Table 1. Funding for primary care initiatives



HHS Strategizes to Improve Care of Patients with Multiple Chronic Conditions

By Rachel Shaffer

The Department of Health and Human Services (HHS) recently launched an initiative to address increasing concerns about the public health impact of the growing number of Americans with multiple chronic conditions.

Approximately 75 million Americans have multiple chronic conditions, including kidney disease, heart disease, and diabetes. Nearly 30 million Americans—13 percent of the population—have chronic kidney disease (CKD). CKD is a common co-morbid condition among patients with other chronic conditions, particularly hypertension, cardiovascular disease, congestive heart failure, diabetes, and peripheral vascular disease. As a patient's number of chronic conditions increases, so too does his or her risk of unnecessary hospitalizations, duplicate tests, conflicting medical advice, and mortality. Today, 66 percent of all health care spending is directed toward care for the approximately 27 percent of Americans

with multiple chronic conditions, according to HHS (Figure 1). Medicare spends \$42 billion annually to treat people with CKD alone—yet it remains the ninth leading cause of death (1,2).

Given the increasing costs of, poor outcomes among, and complexity of managing care for people with multiple chronic conditions—and the leading role HHS plays in health research and payment for and delivery of health care services—HHS recently organized a workgroup on individuals with multiple chronic conditions. This workgroup, which included representatives from nearly every HHS operating division, drafted a “Strategic Framework on Multiple Chronic Conditions (MCC).” Intended to help the department prevent and improve quality of life for individuals with multiple chronic conditions, the draft framework identified opportunities for HHS to take a more coordinated, comprehensive approach to care internally and in collaboration with

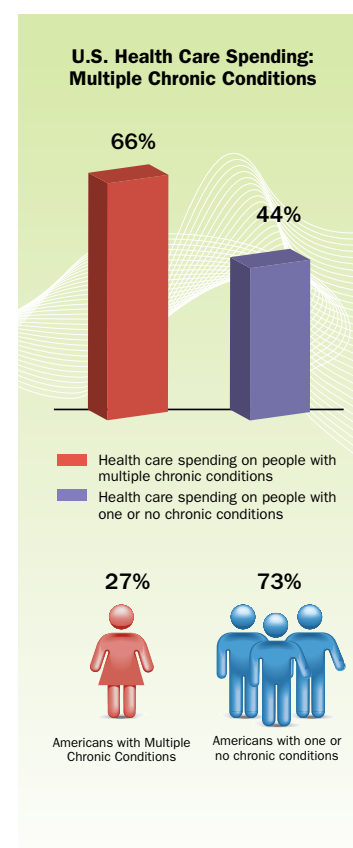
external stakeholders.

Responding to HHS' request for public feedback on the draft framework, ASN President Sharon Anderson, MD, FASN, submitted a comment letter on behalf of the society, drafted in conjunction with the Public Policy Board and ASN staff. In its comments, the society applauded HHS's initiative of improving the health and quality of life for individuals with concurrent chronic conditions, but emphasized the importance of including kidney disease. The initial draft did not include mention of CKD or end stage renal disease.

The ASN Public Policy Board looks forward to collaborating with HHS in its efforts to improve outcomes for patients with multiple chronic conditions—including kidney disease—and will continue to advocate for recognition and inclusion of kidney disease throughout the department's divisions. Read ASN's comment letter online at http://www.asn-online.org/policy_and_public_affairs/. ●

Figure 1.

Percentage of Americans with multiple chronic conditions versus total spending on multiple chronic conditions.



Introducing the ASN Career Center

ASN Members Can Search Jobs for Free!

The ASN Career Center is now open and available to ASN members. Featuring robust candidate and recruiter account modules, the ASN Career Center allows ASN members to easily search jobs, post resumes, review candidates, and apply for positions—all from one site. No matter where ASN members are in their careers, the ASN Career Center has the tools to help all members move to the next level.

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Detective Nephron



Detective Nephron, world-renowned for expert analytical skills, trains budding physician-detectives on the diagnosis and treatment of kidney diseases. L.O. Henle presents a new case to the master consultant.

Henle I have a case for us. Metabolic alkalosis.

Nephron Excellent.

Henle, prepared A 65-year-old male was just seen recently for fatigue and muscle weakness and found to have a serum bicarbonate level of 39 mEq.

Nephron, chuckling Give me a break, apprentice, this is a cake walk. Give some hydration and send him home.

Henle, with a curious look They tried that for three days. Perhaps you want to know that his pre- and posthydration urine chloride values are on or about 80 mEq/L

Nephron, confused Ahhah!, this is going to be fun!

Henle He has recently diagnosed prostate cancer, with metastatic disease to the liver and the bone. He was treated with leuprolide, and recently with cisplatin and etoposide.

The detective listens.
All of a sudden, a knock is heard, and a medical student in a nicely ironed short white coat enters the room.
She appears frightened.

Nephron Who are you and what do you want?

Henle, smirking She is a medical student who has been involved with this case. She wanted to join us today with our discussion. Her name is Ms. Curious Tubule.

Nephron Hello, Ms. Tubule, so here we have a case of metabolic alkalosis or alkalemia?

Tubule He did get an arterial blood gas that revealed a ph of 7.57 and pCO₂ of 41 mm Hg. The bicarbonate was 38. This suggests a case of mixed respiratory and metabolic alkalosis.

Nephron How so?

Henle His primary problem appears to be metabolic alkalosis, and to compensate, his pCO₂ should have been lower, at least 0.5 mm Hg for every rise of bicarbonate of 1 mEq/L. Hence, there is a respiratory alkalosis as well.

Nephron Great job, let's move on. Let's discuss the causes of this patient's metabolic alkalosis. Can either of you tell me why this patient's plasma bicarbonate level rose to 39?

Henle Two possibilities: either there was decreased effective extracellular volume or there was an exogenous or endogenous source of increased extracellular volume content.

Tubule That is so confusing. But wouldn't the urine chloride be helpful here? Since it's high, I don't think it's a low volume state.

Henle I am getting to that point. You can have a low volume state with diuretic use and have a high urine chloride. So don't assume that just because the urine chloride is high, it's not low effective volume yet.

Nephron You are both correct. Fascinating. So now what do we need to do? Find out if he is on a diuretic or taking any endogenous medications that might be increasing his HCO₃ load?

Tubule He refused to take any of the drugs you mention.

Nephron Are you sure? Go back and check again. It's very important to make sure.

Tubule and Henle exit and Detective Nephron resumes drinking his coffee.

Nephron (to himself) Henle and Tubule really were having a very powerful discussion. I love their passion for the subject.

Henle returns to the office.

Nephron You're back.

Henle, very excited No diuretics.

Nephron Good!

Henle But we noticed a few more things: worsening hypokalemia (2.9 mmol/L) and hypernatremia (147 mmol/L), and this has been getting worse for the past month.

Nephron Stop right there! So now you are telling me we have a case of a chloride-resistant hypokalemic metabolic alkalosis?

Henle Yes, you are correct.

Nephron, with confidence I assume normal renal function.

Henle Yes, as usual you are correct.

Nephron, looking around Where is your friend, Ms Tubule?

Henle She is gathering some more data for us. I asked her to get the blood pressure readings for the last few months.

They pause as Tubule enters.

Nephron Let me guess, recent onset of hypertension as well?

The detective pauses to see their response.

Tubule Yes, you are correct.

Nephron

When the urine chloride is not zero, you asked if he was taking a diuretic; you said he wasn't. So now we are left with the question of whether he has hypertension or no hypertension. If he has no hypertension, you enter the world of "Bartter's and friends." You also confirmed normal renal function, another possibility if there was no hypertension.

Henle

The presence of hypertension is important because it might be the only clue to a diagnosis of primary hyperaldosteronism, renal artery stenosis, or production of endogenous compounds in the body that can raise blood pressure and have profound metabolic derangements.

Tubule

So you think he has a primary aldosteronism or something like that?

Nephron, pleased

Excellent. By the way, does he have elevated blood sugars?

Henle

As a matter of fact, he did mention that he was diagnosed recently by his oncologist with type II diabetes mellitus and he has been gaining weight. He had normal blood glucose levels as of last year and he sees a primary care physician regularly.

Tubule

Is that a recent onset diabetes? That is strange?

Henle

So we have a chloride-resistant, hypertensive metabolic alkalosis with hyperglycemia and hypokalemia. Could he have Cushing's syndrome or disease?

Nephron, with a smirk Again, my dear apprentices, I have a diagnosis for you! Perhaps you are correct.

Henle

His plasma renin and serum aldosterone levels were low. His urinalysis revealed >1000 glucose, and urine potassium was 45 mmol/L for a serum potassium of 2.9 mmol/L. He is having renal losses of potassium.

Tubule

Perhaps he is producing too much ACTH? Or too much cortisol?

Nephron

What are you waiting for, you want to check the levels? I shall see you in a few days.

Tubule and Henle exit and Detective Nephron starts reading ASN Kidney News. A few days later...

Nephron

My coffee is good, less sweet than usual.

Tubule

Sweet is the key word. ACTH level was significantly elevated with a 24-hour urinary cortisol level in the astronomical range.

Henle

So this patient is producing ACTH? Where?

Nephron

Did you see his prostate biopsy? He probably has neuroendocrine features and is producing ACTH. I would start ketoconazole soon. Perhaps his ACTH production could be a marker of his cancer.

Tubule

Fascinating!

A few weeks later...

Henle

Dr. Nephron, his prostate cancer is producing ACTH. The octeotide scan and immunohistochemistry staining for ACTH on the prostate biopsy confirmed it. He is responding very well to the therapy. His hypertension, diabetes, alkalosis, and hypokalemia all resolved with the treatment.

Nephron

Remember, this patient presented with Cushing's like syndrome. In patients with the classic form of ectopic ACTH syndrome, the degree of ACTH and urinary cortisol and hypokalemia is much greater than classic Cushing's disease (pituitary cause). Usually ACTH ectopic production is classically seen in small cell and non-small cell lung cancer, but there are cases of thyroid cancer, prostate cancer, and ovarian carcinoid that have been reported with ectopic ACTH production.

Tubule

In ectopic ACTH production, is the hypertension more profound?

Nephron, smiling

Good question. Cushing's syndrome is the cause of hypertension in approximately one in 400 hypertensives. Among patients with Cushing's syndrome, hypertension is very common, affecting some 80 percent of patients. The number of patients with ectopic ACTH production who are hypertensive is usually lower than in other forms of Cushing's syndrome. This is likely due to the shorter duration of the disease or the underlying cancer. No one knows really. As you saw, this patient had hypernatremia, hypokalemia, and initial sodium retention. You see this when there is excess glucocorticoid effect. There is increased urinary retention leading to increased extracellular volume, and there is volume-mediated hypertension. The plasma renin activity will be low. Cortisol, a classic glucocorticoid hormone, might have some mineralocorticoid activity and hence raise blood pressure through its hypertensinogenic activity. These are the two mechanisms usually that can lead to hypertension in ACTH elevations—but again, usually lower chances in ectopic ACTH than in primary Cushing's disease.

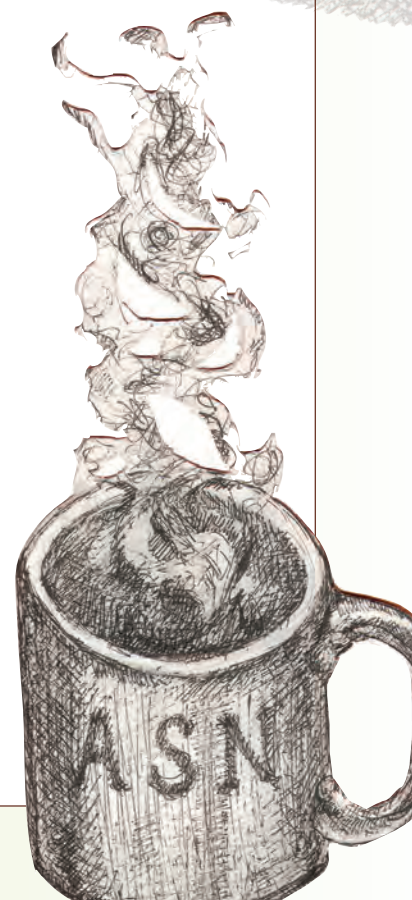
Henle

He is doing very well. His cancer is stable with no further progression.

Nephron

Again, my dear apprentices, from a diagnosis of metabolic alkalosis, you made a diagnosis of a life-threatening systemic disorder. Always be a good detective. Observe, think, read, and apply. If it doesn't cross your mind, you will never diagnosis it. Great case, Henle. ●

Detective Nephron was developed by Kenar Jhaveri, MD, assistant professor of medicine at Hofstra Medical School and an attending nephrologist at North Shore University and Long Island Jewish Medical Center in Great Neck, NY. The column was inspired by Muthukumar Thangamani, MD, and Alan Weinstein, MD, both of Cornell University, and Mitch Halperin, MD, of the University of Toronto. Send correspondences regarding this section to kjhaveri@nshs.edu or kdj200@gmail.com.



Patient Safety: General Principles and the Role of the Nephrologist

By Henry Crevensten and Robert Wachter

As medical professionals, the last thing we want is for patients to come to harm because they came to us for care. Sadly, this happens with alarming regularity. An estimated 44,000 to 98,000 patients die each year as a result of preventable medical errors (1). Thankfully, we as a profession are starting to come together to improve our systems of care in the name of patient safety.

This article provides an overview of several philosophies of patient safety and suggests methods for incorporating these ideas into daily practice.

Until the patient safety movement, most errors were approached as manifestations of individual carelessness. Such errors were dealt with by finger pointing and blaming the individual, or “name and shame.” One of the first concepts to emerge in quality improvement and patient safety was the idea of “systems thinking”—recognizing that most errors result from faulty systems rather than flawed individuals (1).

Reason’s “Swiss cheese model” has provided a useful mental model for thinking about systems versus individuals: while an error chain may involve a slip by an individual, detailed analysis of most errors (often called “root cause analysis”) demonstrates that errors reach patients because multiple layers of potential protection fail. In the analogy, the error makes it through holes in Swiss cheese (see Figure 1).

The Swiss cheese model is helpful because it forces us to focus on tightening the system rather than trying to get people to be perfect. Examples of a systems focus include developing checklists and other memory aides, building in double checks and other redundancies, standardizing practice settings, and implementing computerized decision support or pre-written orders (2). Providers can help by using such systems and becoming involved in their development.

Because our health care system has become so complex, teamwork and communication are vital to the delivery of safe medical care. Teamwork can involve ensuring accurate patient identification (such as using two patient identifiers, helping to prevent the errors that occur when one says “bring the patient in 23A down to interventional radiology”—what if the patient in 23A had been moved?), writing clear orders (using computerized order entry if available), verifying orders (using bar-coding systems), verifying patient medications, or clearly discussing discharge instructions (a major source of error).

In the face of work hour restrictions for residents and more shift work by practicing physicians, thorough handoff communication has become vital to ensuring safe care. Physicians can help by participating or starting teams that collaborate in patient care. Ideally, these teams will be multidisciplinary, including nurses, pharmacists, technicians, and dieticians.

While the focus on systems rather than

individuals has been extraordinarily helpful to promoting safety, there are some areas of patient safety in which our systems are mature yet problems remain. In these areas, we do rely on individual performance. One example is infection control. Many health care organizations have done a good job of improving the systems to support hand hygiene. In many hospitals, there are now ubiquitous hand-washing stations and posters of leading clinicians cleaning their hands. Computerized screen savers graphically illustrate serious health care-associated infections. Yet despite these interventions and associated provider education, only about 70 percent of providers consistently wash their hands before touching patients (3). The concept of “just culture” delineates “blameless acts” (innocent mistakes made by competent providers) versus “blame-worthy acts” (willful violations of safety rules, such as hand hygiene) (4). The patient safety field is increasingly focusing on how to ensure a systems focus for blameless acts while creating accountability when appropriate (5).

Nephrologists may see patients throughout hospitals and outpatient settings, but they also work in a special area—the dialysis center. Particular patient safety issues here include proper identification of the patient, proper use of dialysis orders, adhering to infection control standards (particularly important given the number of procedures and the frequency of serious infections in this population) and using checklists when inserting dialysis catheters. They also care for a special patient population: those with chronic kidney disease. Patients with chronic kidney disease are 19 percent more likely to suffer a preventable medical error than other patients (6), likely as a result of their high rates of hospitalization, procedures, and medications. Nephrologists should at least be aware that their patient population is especially susceptible to errors and be sure to develop and use systems to prevent them.

Lastly, you cannot improve what you do not measure. Most health care systems have some sort of medical error reporting system. This should be used for all types of incidents, not just those that caused harm. The ideal purpose of reporting errors is not only to respond to errors but ultimately to help prevent their occurrence. For example, a large number of reports of mislabeled specimens may indicate a systematic problem in specimen handling that needs to be addressed.

The patient safety field recently marked its 10th anniversary: the Institute of Medicine Report on safety (“To Err is Human”) was released in late 1999. Over the past decade, we have made considerable progress in developing and implementing safety systems, in research in patient safety, and in creating a policy environment in which organizations and individual caregivers are pushed to focus on delivering safe, high-quality care. Given the high risk for

errors among patients with kidney disease, nephrologists have a critical role in developing and implementing safety systems, and ensuring that such systems help meet the specific needs of their patients and settings of care. ●

Henry Crevensten, MD, is assistant professor in the department of medicine and Robert Wachter, MD, is professor and chief of the division of hospital medicine at the University of California, San Francisco.

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Additional Resources

Internet

1. The Joint Commission (www.jointcommission.org)
2. Keeping Kidney Patients Safe, a resource of the Renal Physicians Association (www.kidneypatientsafety.org)
3. Institute for Health Care Improvement (www.ihc.org)
4. Agency for Health Care Research and Quality (www.ahrq.gov)

Publications

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Figure 1. Reason’s “Swiss cheese” model of error

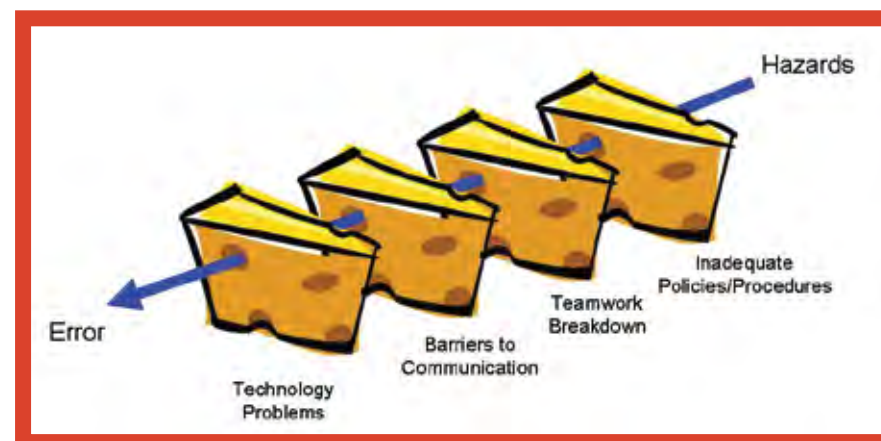


Figure 2. As settings of care become more and more complex, the importance of creating safe systems grows.



Photo courtesy of Michael Gropper, MD, PhD

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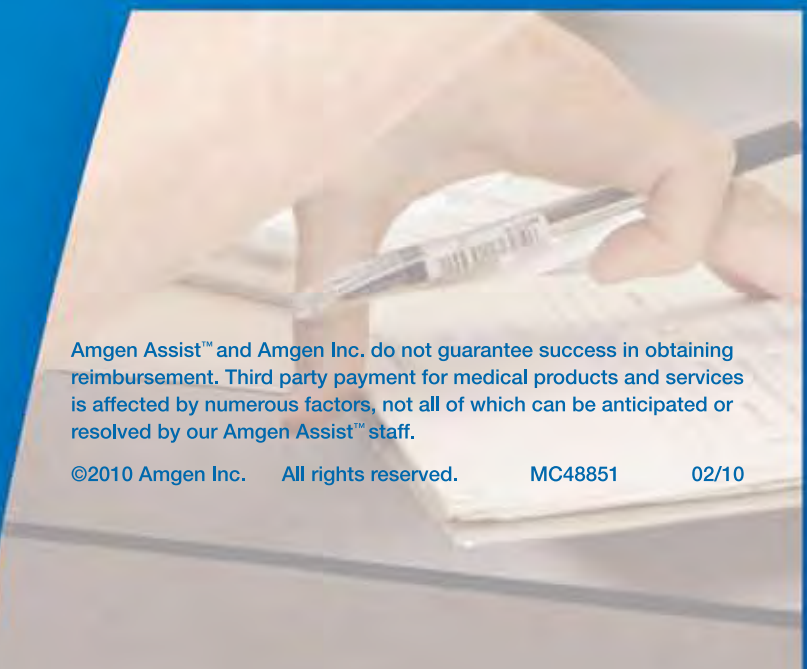
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