ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Kidney News

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Italian Nephrologists Invent Renal Replacement Machine for Neonates

Some of the smallest infants with acute kidney injury (AKI) can now seize the day—with a dialysis system specifically designed for them. The Cardio-Renal Pediatric Dialysis Emergency Machine (CARPEDIEM) is the first continuous renal replacement therapy (CRRT) designed for neonates.

Speaking at the European Renal Association—European Dialysis and Transplant Association conference in Amsterdam, Claudio Ronco, MD, of the International Renal Research Institute at San Bortolo Hospital in Vicenza, Italy, said that current CRRT systems are often used off-label for infants smaller than 15 kg but are not ideal.

CARPEDIEM, designed for infants weighing 2.5–10 kg, addresses many of the problems with the bigger machines by using a circuit with a priming volume of 27 mL including filter, miniaturized roller pumps providing a flow as low as 5–50 mL/min, and accurate ultrafiltration with a precision of 1 g. Filters with three different surface areas can accommodate patients of different sizes. Laboratory testing showed quite low levels of microhemolysis. The research team's work was published in *The Lancet* on May 24.

"It definitely has been needed for a long time," Benjamin Laskin, MD, MS, assistant professor of pediatrics in nephrology at Children's Hospital of Philadelphia, told *ASN Kidney News*. Adult machines that are approved for patients weighing more than 20 kg have been adapted for infants, "but there are some limitations," such as needing to prime with more blood and alarms calibrated for larger individuals.

CARPEDIEM provides more options than peritoneal dialysis

After completing a 5-year development project, including in vitro testing of the system, meeting regulatory requirements, and then licensing for human use, the clinicians at San Bortolo Hospital treated a 2.9-kg neonate with hemorrhagic shock, multiorgan dysfunction, and severe fluid overload with CARPEDIEM for more than 400 hours using continuous venovenous hemofiltration, single-pass albumin dialysis, blood exchange, and plasma exchange.

The CRRT was started at 3 days after birth. The neonate's fluid overload was 63 percent, with a body weight of 5.2 kg. Physicians placed a dual-lumen 22 gauge

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Annual Round of Proposed Changes to ESRD Program Includes Expected, and Unexpected, Proposals

By Rachel Meyer and Mark Lukaszewski

Fourth of July weekend: parades, barbecues, fireworks—and the annual release of proposed revisions to the Medicare ESRD End-Stage Renal Disease (ESRD) Prospective Payment System (PPS) and Quality Incentive Program (QIP). On Wednesday, July 2, the Centers for Medicare & Medicaid Services (CMS) released its proposed rule recommending changes to the ESRD program, adding 359 pages of federal regulations to ASN's Public Policy Board's and Quality Metrics Task Force's holiday weekend reading.

Since then, the task force and policy board assessed proposed changes to both payments for dialysis care and modifications to the mandatory quality program. Several key areas of interest—both positive and negative—are summarized here; further analyses will be posted on ASN's website. The society will provide CMS with detailed recommendations for improvement to ensure patients continue to have access to the highest quality care possible within the Medicare ESRD program.

Key proposed changes to the bundle

Most of the changes CMS proposes for

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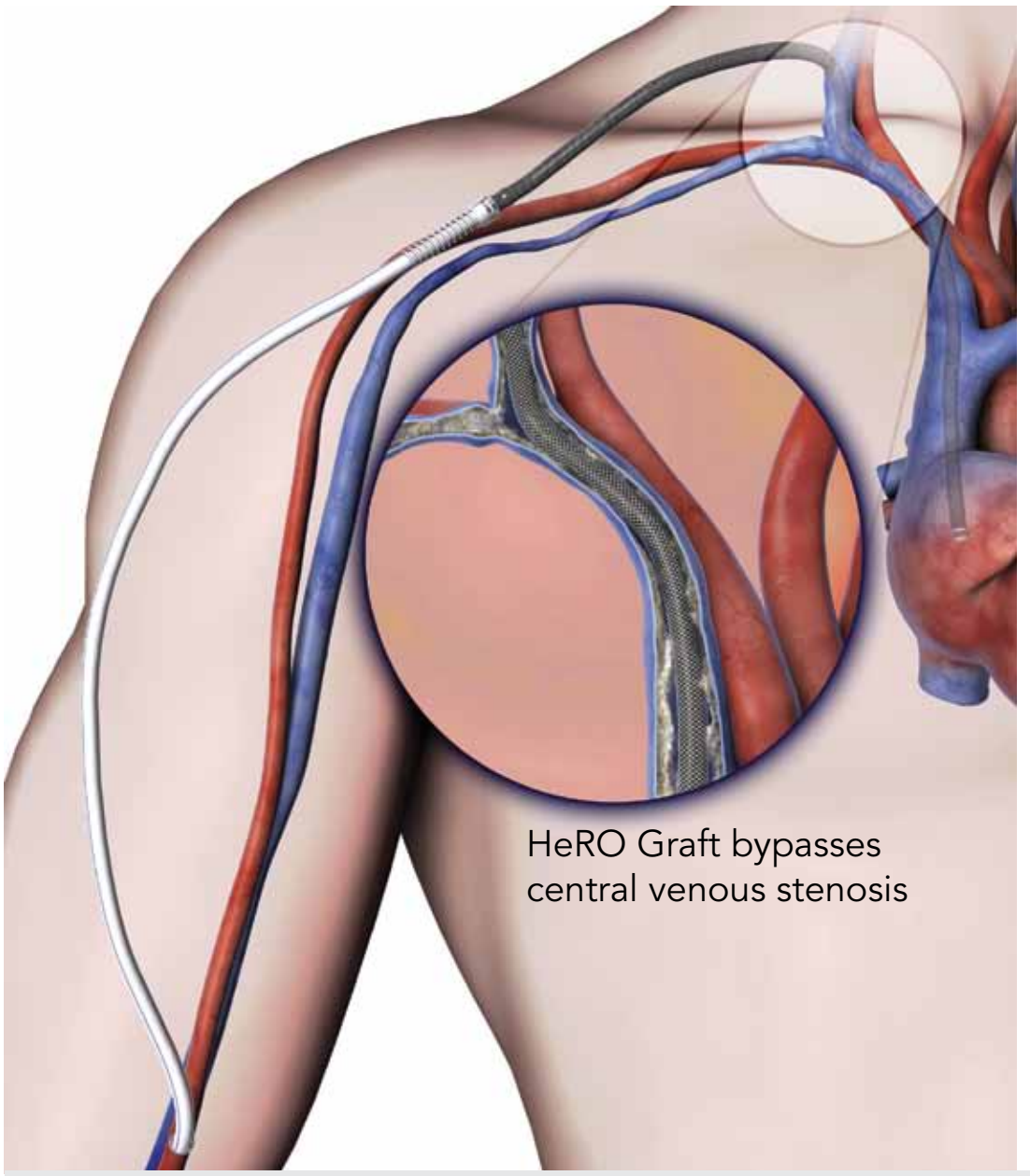

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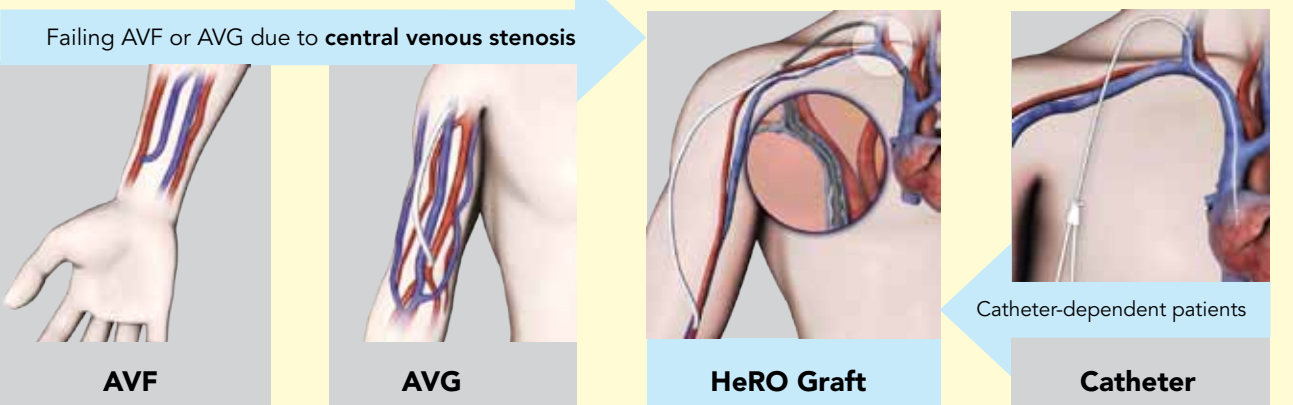

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References:
1) Katzman et al., J Vasc Surg 2009. 2) Gage et al., EJVES 2012. 3) Dageforde et al., JSR 2012.

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(4 French) catheter into the femoral vein and began postdilution continuous venovenous hemofiltration with CARPEDIEM at a flow rate of 9–13 mL/min and a daily clearance between 2.2 and 2.8 L, which was an exchange volume close to the patient's total body water.

The researchers reported that there was no clotting or functional decay in the circuit, nor did any blood contact reactions occur during treatments.

By day 10, the fluid overload was brought down to 33 percent, and at the end of CRRT on day 25 it was 12 percent. Similarly, serum creatinine and bilirubin concentrations and severe acidosis were all managed safely and effectively. The baby was discharged from the hospital at 59 days of age with some mild renal insufficiency that did not require renal replacement therapy.

The researchers concluded that CRRT with CARPEDIEM is "feasible, accurate, and safe." They advised that dual-lumen catheters smaller than 7 or 8 French, often the smallest available, need to be developed.

Incidence of neonatal AKI higher than previously estimated

The incidence of neonatal AKI has been underestimated at about 1–2 percent for many years. But in neonates weighing more than 2 kg and admitted to neonatal intensive care units, the incidence has been estimated in one study at 16 percent, and it may be much higher than that.

Timothy Bunchman, MD, professor and director of pediatric nephrology at Virginia Commonwealth University School of Medicine in Richmond and co-chair of an April 2013 National Institutes of Health workshop on neonatal AKI, told *ASN Kidney News*, "The incidence is huge. It's anywhere between 10 to 80 percent, depending on what population you look at and literature you use." Of those, "maybe only 5 percent" require dialysis.

But that 5 percent is still a large niche for which options have been lacking. "It's a breakthrough in an area that's very difficult," Bunchman said.

Peritoneal dialysis (PD) will still be the treatment of choice for most infants needing renal replacement therapy. "But we can't use it in all situations," said Laskin, who wrote an editorial to accompany *The Lancet* article. He cited situations in which neonates have had abdominal surgery, instances in which metabolic toxins or electrolytes such as potassium need to be removed quickly, or cases of toxic ingestions in which PD does not work as well as hemodialysis.

Besides continuous venovenous hemofiltration, CARPEDIEM can extend the range of extracorporeal treatments, allowing continuous venovenous hemodiafiltration, plasma exchange, blood exchange, and single-pass albumin dialysis, and also provide fluid management after cardiac surgery.

CARPEDIEM advantages and cautions

Bunchman said that a system with a 52-mL extracorporeal circuit is approved in Europe, "but the CARPEDIEM is literally half that volume. It's 27 milliliters…. It allows one to safely and easily do extracorporeal therapies in kids probably down to about 2 kilos."

But he thinks that problems with typical larger catheters may be magnified with the smaller ones. "You can have hemolysis. Literally placing the thing is the difficult part—getting a small catheter in some of these small guys," he said. "So placement, flow characteristics, destruction [of blood elements], occlusion, clotting, infection—all those are risk factors associated with the smaller catheters."

On the other hand, lower-volume circuits can be a good thing. Laskin said that CARPEDIEM avoids problems associated with larger circuits. "Number one, giving the blood when you prime can cause bradykinin release, which can lead to hypotension," he noted, "and in the long term, we think, we don't know, that the more blood products that we expose these kids to may increase their risk of getting sensitized for later transplants."

The machine appears to remove fluid well, but Laskin said the researchers still need to validate that it adequately clears solutes at lower flow rates and with small catheters. "It will be important in babies that are anuric to make sure we're removing enough toxins, too."

Both Laskin and Bunchman said they were disappointed that the research report involved only one patient. "Through the rumor mill, I know they've used it on four or five kids," Bunchman said.

Although PD will remain the most commonly used form of dialysis in infants worldwide because of simplicity and access to resources, "This actually will add a niche, but in only certain countries" with higher incomes and a high level of medical sophistication, said Bunchman. He advised that more nondialytic therapies need to be developed, some of which are already coming along. Even in richer, more developed countries, "This is not going to be in the community [hospitals]. This is going to be at university and tertiary-based centers completely," he predicted.

Even there, and considering that "the pediatric neonatologists are very excited," Bunchman foresees that neonatologists may be a barrier to the adoption of a system like CARPEDIEM. "This is a foreign concept to neonatologists. It's just outside their comfort zone," he said. But a device specifically designed for some of the smallest patients and that avoids jury-rigging adult dialysis machines may in the end help to raise neonatologists' comfort level and lessen their resistance.

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- **Too rapid correction of serum sodium can cause serious neurologic sequelae**
- **Avoid fluid restriction during the first 24 hours of therapy**

INDICATION and Important Limitations

- SAMSCA is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH)
- Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with SAMSCA. It has not been established that raising serum sodium with SAMSCA provides a symptomatic benefit to patients

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SAMSCA should be initiated and re-initiated in patients only in a hospital where serum sodium can be monitored closely. Too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable

Contraindications: Urgent need to raise serum sodium acutely, inability of the patient to sense or appropriately respond to thirst, hypovolemic hyponatremia, concomitant use of strong CYP 3A inhibitors, anuric patients, and hypersensitivity (e.g. anaphylactic shock, rash generalized) to tolvaptan or its components

Warnings and Precautions:

- Subjects with SIADH or very low baseline serum sodium concentrations may be at greater risk for too-rapid correction of serum sodium. In patients receiving SAMSCA who develop too rapid a rise in serum sodium or develop neurologic sequelae, discontinue or interrupt treatment with SAMSCA and consider administration of hypotonic fluid. Fluid restriction should generally be avoided during the first 24 hours
- SAMSCA can cause serious and potentially fatal liver injury. Avoid use in patients with underlying liver disease, including cirrhosis, because the ability to recover may be impaired. Limit duration of therapy with SAMSCA to 30 days
- Dehydration and hypovolemia can occur, especially in potentially volume-depleted patients receiving diuretics or those who are fluid restricted. In patients who develop medically significant signs or symptoms of hypovolemia, discontinuation is recommended
- Co-administration with hypertonic saline is not recommended
- Avoid concomitant use with: CYP 3A inhibitors and CYP 3A inducers. The dose of SAMSCA may have to be reduced if co-administered with P-gp inhibitors
- Monitor serum potassium levels in patients with a serum potassium >5 mEq/L and in patients receiving drugs known to increase serum potassium levels

Adverse Reactions - The most common adverse reactions (SAMSCA incidence ≥5% more than placebo, respectively): thirst (16% vs 5%), dry mouth (13% vs 4%), asthenia (9% vs 4%), constipation (7% vs 2%), pollakiuria or polyuria (11% vs 3%) and hyperglycemia (6% vs 1%)

Gastrointestinal Bleeding in Patients with Cirrhosis – In patients with cirrhosis in the hyponatremia trials, GI bleeding was reported in 10% of tolvaptan-treated patients vs 2% for placebo

Please see Brief Summary of FULL PRESCRIBING INFORMATION, including Boxed WARNING, on following page.

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INDICATIONS AND USAGE: SAMSCA is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).
Important Limitations: Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with SAMSCA. It has not been established that raising serum sodium with SAMSCA provides a symptomatic benefit to patients.
CONTRAINDICATIONS: SAMSCA is contraindicated in the following conditions:
Urgent need to raise serum sodium acutely: SAMSCA has not been studied in a setting of urgent need to raise serum sodium acutely.
Inability of the patient to sense or appropriately respond to thirst: Patients who are unable to auto-regulate fluid balance are at substantially increased risk of incurring an overly rapid correction of serum sodium, hypernatremia and hypovolemia.
Hypovolemic hyponatremia: Risks associated with worsening hypovolemia, including complications such as hypotension and renal failure, outweigh possible benefits.
Concomitant use of strong CYP 3A inhibitors: Ketoconazole 200 mg administered with tolvaptan increased tolvaptan exposure by 5-fold. Larger doses would be expected to produce larger increases in tolvaptan exposure. There is not adequate experience to define the dose adjustment that would be needed to allow safe use of tolvaptan with strong CYP 3A inhibitors such as clarithromycin, ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, and telithromycin.
Anuric patients: In patients unable to make urine, no clinical benefit can be expected.
Hypersensitivity: SAMSCA is contraindicated in patients with hypersensitivity (e.g. anaphylactic shock, rash generalized) to tolvaptan or any component of the product *[see Adverse Reactions (6.2)]*.
WARNINGS AND PRECAUTIONS:
Too Rapid Correction of Serum Sodium Can Cause Serious Neurologic Sequelae (see BOXED WARNING): Osmotic demyelination syndrome is a risk associated with too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours). Osmotic demyelination results in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma or death. In susceptible patients including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable. In controlled clinical trials in which tolvaptan was administered in titrated doses starting at 15 mg once daily, 7% of tolvaptan-treated subjects with a serum sodium <130 mEq/L had an increase in serum sodium greater than 8 mEq/L at approximately 8 hours and 2% had an increase greater than 12 mEq/L at 24 hours. Approximately 1% of placebo-treated subjects with a serum sodium <130 mEq/L had a rise greater than 8 mEq/L at 8 hours and no patient had a rise greater than 12 mEq/L/24 hours. Osmotic demyelination syndrome has been reported in association with SAMSCA therapy *[see Adverse Reactions (6.2)]*. Patients treated with SAMSCA should be monitored to assess serum sodium concentrations and neurologic status, especially during initiation and after titration. Subjects with SIADH or very low baseline serum sodium concentrations may be at greater risk for too-rapid correction of serum sodium. In patients receiving SAMSCA who develop too rapid a rise in serum sodium, discontinue or interrupt treatment with SAMSCA and consider administration of hypotonic fluid. Fluid restriction during the first 24 hours of therapy with SAMSCA may increase the likelihood of overly-rapid correction of serum sodium, and should generally be avoided.
Liver Injury: SAMSCA can cause serious and potentially fatal liver injury. In a placebo-controlled and open label extension study of chronically administered tolvaptan in patients with autosomal dominant polycystic kidney disease, cases of serious liver injury attributed to tolvaptan were observed. An increased incidence of ALT greater than three times the upper limit of normal was associated with tolvaptan (42/958 or 4.4%) compared to placebo (5/484 or 1.0%). Cases of serious liver injury were generally observed starting 3 months after initiation of tolvaptan although elevations of ALT occurred prior to 3 months. Patients with symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice should discontinue treatment with SAMSCA. Limit duration of therapy with SAMSCA to 30 days. Avoid use in patients with underlying liver disease, including cirrhosis, because the ability to recover from liver injury may be impaired. *[see Adverse Reactions (6.1)]*.
Dehydration and Hypovolemia: SAMSCA therapy induces copious aquaresis, which is normally partially offset by fluid intake. Dehydration and hypovolemia can occur, especially in potentially volume-depleted patients receiving diuretics or those who are fluid restricted. In multiple-dose, placebo-controlled trials in which 607 hyponatremic patients were treated with tolvaptan, the incidence of dehydration was 3.3% for tolvaptan and 1.5% for placebo-treated patients. In patients receiving SAMSCA who develop medically significant signs or symptoms of hypovolemia, interrupt or discontinue SAMSCA therapy and provide supportive care with careful management of vital signs, fluid balance and electrolytes. Fluid restriction during therapy with SAMSCA may increase the risk of dehydration and hypovolemia. Patients receiving SAMSCA should continue ingestion of fluid in response to thirst.
Co-administration with Hypertonic Saline: Concomitant use with hypertonic saline is not recommended.
Drug Interactions:
Other Drugs Affecting Exposure to Tolvaptan:
CYP 3A Inhibitors: Tolvaptan is a substrate of CYP 3A. CYP 3A inhibitors can lead to a marked increase in tolvaptan concentrations *[see Dosage and Administration (2.3), Drug Interactions (7.1)]*.
Do not use SAMSCA with strong inhibitors of CYP 3A *[see Contraindications (4.4)]* and avoid concomitant use with moderate CYP 3A inhibitors.
CYP 3A Inducers: Avoid co-administration of CYP 3A inducers (e.g., rifampin, rifabutin, rifapentin, barbiturates, phenytoin, carbamazepine, St. John's Wort) with SAMSCA, as this can lead to a reduction in the plasma concentration of tolvaptan and decreased effectiveness of SAMSCA treatment. If co-administered with CYP 3A inducers, the dose of SAMSCA may need to be increased *[see Dosage and Administration (2.3), Drug Interactions (7.1)]*.
P-gp Inhibitors: The dose of SAMSCA may have to be reduced when SAMSCA is co-administered with P-gp inhibitors, e.g., cyclosporine *[see Dosage and Administration (2.3), Drug Interactions (7.1)]*.
Hyperkalemia or Drugs that Increase Serum Potassium: Treatment with tolvaptan is associated with an acute reduction of the extracellular fluid volume which could result in increased serum potassium. Serum potassium levels should be monitored after initiation of tolvaptan treatment in patients with a serum potassium >5 mEq/L as well as those who are receiving drugs known to increase serum potassium levels.
ADVERSE REACTIONS:
Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reactions 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. The adverse event information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates. In multiple-dose, placebo-controlled trials, 607 hyponatremic patients (serum sodium <135 mEq/L) were treated with SAMSCA. The mean age of these patients was 62 years; 70% of patients were male and 82% were Caucasian. One hundred eighty nine (189) tolvaptan-treated patients had a serum sodium <130 mEq/L, and 52 patients had a serum sodium <125 mEq/L. Hyponatremia was attributed to cirrhosis in 17% of patients, heart failure in 68% and SIADH/other in 16%. Of these patients, 223 were treated with the recommended dose titration (15 mg titrated to 60 mg as needed to raise serum sodium). Overall, over 4,000 patients have been treated with oral doses of tolvaptan in open-label or placebo-controlled clinical trials. Approximately 650 of these patients had hyponatremia; approximately 219 of these hyponatremic patients were treated with tolvaptan for 6 months or more. The most common adverse reactions (incidence ≥5% more than placebo) seen in two 30-day, double-blind, placebo-controlled hyponatremia trials in which tolvaptan was administered in titrated doses (15 mg to 60 mg once daily) were thirst, dry mouth, asthenia, constipation, pollakiuria or polyuria and hyperglycemia. In these trials, 10% (23/223) of tolvaptan-treated patients discontinued treatment because of an adverse event, compared to 12% (26/220) of placebo-treated patients; no adverse reaction resulting in discontinuation of trial medication occurred at an incidence of >1% in tolvaptan-treated patients.
Table 1 lists the adverse reactions reported in tolvaptan-treated patients with hyponatremia (serum sodium <135 mEq/L) and at a rate at least 2% greater than placebo-treated patients in two 30-day, double-blind, placebo-controlled trials. In these studies, 223 patients were exposed to tolvaptan (starting dose 15 mg, titrated to 30 and 60 mg as needed to raise serum sodium). Adverse events resulting in death in these trials were 6% in tolvaptan-treated-patients and 6% in placebo-treated patients.

Table 1. Adverse Reactions (>2% more than placebo) in Tolvaptan-Treated Patients in Double-Blind, Placebo-Controlled Hyponatremia Trials

System Organ Class MedDRA Preferred Term	Tolvaptan 15 mg/day-60 mg/day (N = 223) n (%)	Placebo (N = 220) n (%)
Gastrointestinal Disorders		
Dry mouth	28 (13)	9 (4)
Constipation	16 (7)	4 (2)
General Disorders and Administration Site Conditions		
Thirst[a]	35 (16)	11 (5)
Asthenia	19 (9)	9 (4)
Pyrexia	9 (4)	2 (1)
Metabolism and Nutrition Disorders		
Hyperglycemia[b]	14 (6)	2 (1)
Anorexia[c]	8 (4)	2 (1)
Renal and Urinary Disorders		
Pollakiuria or polyuria[d]	25 (11)	7 (3)

The following terms are subsumed under the referenced ADR in Table 1:
[a]polydipsia; [b]diabetes mellitus; [c]decreased appetite; [d]urine output increased, micturition, urgency, nocturia

In a subgroup of patients with hyponatremia (N = 475, serum sodium <135 mEq/L) enrolled in a double-blind, placebo-controlled trial (mean duration of treatment was 9 months) of patients with worsening heart failure, the following adverse reactions occurred in tolvaptan-treated patients at a rate at least 2% greater than placebo: mortality (42% tolvaptan, 38% placebo), nausea (21% tolvaptan, 16% placebo), thirst (12% tolvaptan, 2% placebo), dry mouth (7% tolvaptan, 2% placebo) and polyuria or pollakiuria (4% tolvaptan, 1% placebo).

Gastrointestinal bleeding in patients with cirrhosis: In patients with cirrhosis treated with tolvaptan in the hyponatremia trials, gastrointestinal bleeding was reported in 6 out of 63 (10%) tolvaptan-treated patients and 1 out of 57 (2%) placebo treated patients.
The following adverse reactions occurred in <2% of hyponatremic patients treated with SAMSCA and at a rate greater than placebo in double-blind placebo-controlled trials (N = 607 tolvaptan; N = 518 placebo) or in <2% of patients in an uncontrolled trial of patients with hyponatremia (N = 111) and are not mentioned elsewhere in the label: *Blood and Lymphatic System Disorders: Disseminated intravascular coagulation; Cardiac Disorders: Intracardiac thrombus, ventricular fibrillation; Investigations: Prothrombin time prolonged; Gastrointestinal Disorders: Ischemic colitis; Metabolism and Nutrition Disorders: Diabetic ketoacidosis; Musculoskeletal and Connective Tissue Disorders: Rhabdomyolysis; Nervous System: Cerebrovascular accident; Renal and Urinary Disorders: Urethral hemorrhage; Reproductive System and Breast Disorders (female): Vaginal hemorrhage; Respiratory, Thoracic, and Mediastinal Disorders: Pulmonary embolism, respiratory failure; Vascular disorder: Deep vein thrombosis.*
Postmarketing Experience: The following adverse reactions have been identified during post-approval use of SAMSCA. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Neurologic: Osmotic demyelination syndrome; *Investigations:* Hypernatremia. Removal of excess free body water increases serum osmolality and serum sodium concentrations. All patients treated with tolvaptan, especially those whose serum sodium levels become normal, should continue to be monitored to ensure serum sodium remains within normal limits. If hypernatremia is observed, management may include dose decreases or interruption of tolvaptan treatment, combined with modification of free-water intake or infusion. During clinical trials of hyponatremic patients, hypernatremia was reported as an adverse event in 0.7% of patients receiving tolvaptan vs. 0.6% of patients receiving placebo; analysis of laboratory values demonstrated an incidence of hypernatremia of 1.7% in patients receiving tolvaptan vs. 0.8% in patients receiving placebo. *Immune System Disorders:* Hypersensitivity reactions including anaphylactic shock and rash generalized *[see Contraindications (4.6)]*.
DRUG INTERACTIONS:
Effects of Drugs on Tolvaptan:
Ketoconazole and Other Strong CYP 3A Inhibitors: SAMSCA is metabolized primarily by CYP 3A. Ketoconazole is a strong inhibitor of CYP 3A and also an inhibitor of P-gp. Co-administration of SAMSCA and ketoconazole 200 mg daily results in a 5-fold increase in exposure to tolvaptan. Co-administration of SAMSCA with 400 mg ketoconazole daily or with other strong CYP 3A inhibitors (e.g., clarithromycin, itraconazole, telithromycin, saquinavir, nelfinavir, ritonavir and nefazodone) at the highest labeled dose would be expected to cause an even greater increase in tolvaptan exposure. Thus, SAMSCA and strong CYP 3A inhibitors should not be co-administered *[see Dosage and Administration (2.3) and Contraindications (4.4)]*.
Moderate CYP 3A Inhibitors: The impact of moderate CYP 3A inhibitors (e.g., erythromycin, fluconazole, aprepitant, diltiazem and verapamil) on the exposure to co-administered tolvaptan has not been assessed. A substantial increase in the exposure to tolvaptan would be expected when SAMSCA is co-administered with moderate CYP 3A inhibitors. Co-administration of SAMSCA with moderate CYP3A inhibitors should therefore generally be avoided *[see Dosage and Administration (2.3) and Warnings and Precautions (5.5)]*. **Grapefruit Juice:** Co-administration of grapefruit juice and SAMSCA results in a 1.8-fold increase in exposure to tolvaptan *[see Dose and Administration (2.3) and Warnings and Precautions (5.5)]*. **P-gp Inhibitors:** Reduction in the dose of SAMSCA may be required in patients concomitantly treated with P-gp inhibitors, such as e.g., cyclosporine, based on clinical response *[see Dose and Administration (2.3) and Warnings and Precautions (5.5)]*. **Rifampin and Other CYP 3A Inducers:** Rifampin is an inducer of CYP 3A and P-gp. Co-administration of rifampin and SAMSCA reduces exposure to tolvaptan by 85%. Therefore, the expected clinical effects of SAMSCA in the presence of rifampin and other inducers (e.g., rifabutin, rifapentin, barbiturates, phenytoin, carbamazepine and St. John's Wort) may not be observed at the usual dose levels of SAMSCA. The dose of SAMSCA may have to be increased *[Dosage and Administration (2.3) and Warnings and Precautions (5.5)]*. **Lovastatin, Digoxin, Furosemide, and Hydrochlorothiazide:** Co-administration of lovastatin, digoxin, furosemide, and hydrochlorothiazide with SAMSCA has no clinically relevant impact on the exposure to tolvaptan.
Effects of Tolvaptan on Other Drugs: Digoxin: Digoxin is a P-gp substrate. Co-administration of SAMSCA with digoxin increased digoxin AUC by 20% and Cmax by 30%. **Warfarin, Amiodarone, Furosemide, and Hydrochlorothiazide:** Co-administration of tolvaptan does not appear to alter the pharmacokinetics of warfarin, furosemide, hydrochlorothiazide, or amiodarone (or its active metabolite, desethylamiodarone) to a clinically significant degree. **Lovastatin:** SAMSCA is a weak inhibitor of CYP 3A. Co-administration of lovastatin and SAMSCA increases the exposure to lovastatin and its active metabolite lovastatin-β hydroxyacid by factors of 1.4 and 1.3, respectively. This is not a clinically relevant change.
Pharmacodynamic Interactions: Tolvaptan produces a greater 24 hour urine volume/excretion rate than does furosemide or hydrochlorothiazide. Concomitant administration of tolvaptan with furosemide or hydrochlorothiazide results in a 24 hour urine volume/excretion rate that is similar to the rate after tolvaptan administration alone. Although specific interaction studies were not performed, in clinical studies tolvaptan was used concomitantly with beta-blockers, angiotensin receptor blockers, angiotensin converting enzyme inhibitors and potassium sparing diuretics. Adverse reactions of hyperkalemia were approximately 1-2% higher when tolvaptan was administered with angiotensin receptor blockers, angiotensin converting enzyme inhibitors and potassium sparing diuretics compared to administration of these medications with placebo. Serum potassium levels should be monitored during concomitant drug therapy. As a V_2 receptor antagonist, tolvaptan may interfere with the V_2 agonist activity of desmopressin (dDAVP). In a male subject with mild Von Willebrand (vW) disease, intravenous infusion of dDAVP 2 hours after administration of oral tolvaptan did not produce the expected increases in vW Factor Antigen or Factor VIII activity. It is not recommended to administer SAMSCA with V_2 agonist.
USE IN SPECIFIC POPULATIONS: There is no need to adjust dose based on age, gender, race, or cardiac function *[see Clinical Pharmacology (12.3)]*.
Pregnancy: Pregnancy Category C. There are no adequate and well controlled studies of SAMSCA use in pregnant women. In animal studies, cleft palate, brachymelia, microphthalmia, skeletal malformations, decreased fetal weight, delayed fetal ossification, and embryo-fetal death occurred. SAMSCA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In embryo-fetal development studies, pregnant rats and rabbits received oral tolvaptan during organogenesis. Rats received 2 to 162 times the maximum recommended human dose (MRHD) of tolvaptan (on a body surface area basis). Reduced fetal weights and delayed fetal ossification occurred at 162 times the MRHD. Signs of maternal toxicity (reduction in body weight gain and food consumption) occurred at 16 and 162 times the MRHD. When pregnant rabbits received oral tolvaptan at 32 to 324 times the MRHD (on a body surface area basis), there were reductions in maternal body weight gain and food consumption at all doses, and increased abortions at the mid and high doses (about 97 and 324 times the MRHD). At 324 times the MRHD, there were increased rates of embryo-fetal death, fetal microphthalmia, open eyelids, cleft palate, brachymelia and skeletal malformations *[see Nonclinical Toxicology (13.3)]*.
Labor and Delivery: The effect of SAMSCA on labor and delivery in humans is unknown.
Nursing Mothers: It is not known whether SAMSCA is excreted into human milk. Tolvaptan is excreted into the milk of lactating rats. Because many drugs are excreted into human milk and because of the potential for serious adverse reactions in nursing infants from SAMSCA, a decision should be made to discontinue nursing or SAMSCA, taking into consideration the importance of SAMSCA to the mother.
Pediatric Use: Safety and effectiveness of SAMSCA in pediatric patients have not been established.
Geriatric Use: Of the total number of hyponatremic subjects treated with SAMSCA in clinical studies, 42% were 65 and over, while 19% 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. Increasing age has no effect on tolvaptan plasma concentrations.
Use in Patients with Hepatic Impairment: Moderate and severe hepatic impairment do not affect exposure to tolvaptan to a clinically relevant extent. No dose adjustment of tolvaptan is necessary. Avoid use of tolvaptan in patients with underlying liver disease.
Use in Patients with Renal Impairment: No dose adjustment is necessary based on renal function. There are no clinical trial data in patients with CrCl <10 mL/min, and, because drug effects on serum sodium levels are likely lost at very low levels of renal function, use in patients with a CrCl <10 mL/min is not recommended. No benefit can be expected in patients who are anuric *[see Contraindications 4.5) and Clinical Pharmacology (12.3)]*.
Use in Patients with Congestive Heart Failure: The exposure to tolvaptan in patients with congestive heart failure is not clinically relevantly increased. No dose adjustment is necessary.
OVERDOSAGE: Single oral doses up to 480 mg and multiple doses up to 300 mg once daily for 5 days have been well tolerated in studies in healthy subjects. There is no specific antidote for tolvaptan intoxication. The signs and symptoms of an acute overdose can be anticipated to be those of excessive pharmacologic effect: a rise in serum sodium concentration, polyuria, thirst, and dehydration/hypovolemia. The oral LD50 of tolvaptan in rats and dogs is >2000 mg/kg. No mortality was observed in rats or dogs following single oral doses of 2000 mg/kg (maximum feasible dose). A single oral dose of 2000 mg/kg was lethal in mice, and symptoms of toxicity in affected mice included decreased locomotor activity, staggering gait, tremor and hypothermia.
If overdose occurs, estimation of the severity of poisoning is an important first step. A thorough history and details of overdose should be obtained, and a physical examination should be performed. The possibility of multiple drug involvement should be considered. Treatment should involve symptomatic and supportive care, with respiratory, ECG and blood pressure monitoring and water/electrolyte supplements as needed. A profuse and prolonged aquaresis should be anticipated, which, if not matched by oral fluid ingestion, should be replaced with intravenous hypotonic fluids, while closely monitoring electrolytes and fluid balance.
ECG monitoring should begin immediately and continue until ECG parameters are within normal ranges. Dialysis may not be effective in removing tolvaptan because of its high binding affinity for human plasma protein (>99%). Close medical supervision and monitoring should continue until the patient recovers.
PATIENT COUNSELING INFORMATION: As a part of patient counseling, healthcare providers must review the SAMSCA Medication Guide with every patient *[see FDA-Approved Medication Guide (17.3)]*.
Concomitant Medication: Advise patients to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs since there is a potential for interactions.**Strong and Moderate CYP 3A inhibitors and P-gp inhibitors:** Advise patients to inform their physician if they use strong (e.g., ketoconazole, itraconazole, clarithromycin, telithromycin, nelfinavir, saquinavir, indinavir, ritonavir) or moderate CYP 3A inhibitors (e.g., aprepitant, erythromycin, diltiazem, verapamil, fluconazol) or P-gp inhibitors (e.g., cyclosporine) *[see Dosage and Administration (2.3), Contraindications (4.4), Warnings and Precautions (5.5) and Drug Interactions (7.1)]*.
Nursing: Advise patients not to breastfeed an infant if they are taking SAMSCA *[see Use In Specific Populations (8.3)]*.
For more information about SAMSCA, call 1-877-726-7220 or go to www.samsca.com.
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ESRD Program

Continued from page 1

the payment bundle were codified in the Protecting Access to Medicare Act of 2014 (PAMA) statute, and, predictably, CMS' interpretation of that law did not come as a surprise to the kidney community. Importantly, PAMA mitigated cuts that Congress had previously called for in the American Taxpayer Relief Act (ATRA)—cuts CMS had proposed to implement by reducing bundled payments by 12 percent. Many in the kidney community, including ASN, had raised serious concerns to Congress and regulators about the negative potential effects a cut of that magnitude could have on patient access to high-quality care, particularly in rural and inner-city areas.

Although CMS proposed to set the base rate for 2015 at $239.33—a zero percent update to the payment rate—the situation is not as dire for patients and providers as it otherwise would have been. Another noteworthy change CMS proposes to implement based on the PAMA statute is delaying adding oral-only drugs to the bundle until the year 2024, previously slated to begin in 2016.

CMS indicated that it would maintain the increase in the home dialysis training adjustment that it implemented last year. This increase brought payments up by $16.72, for a total training add-on adjustment of $50.16 per training treatment. ASN will continue to reaffirm the importance of home dialysis training and highlight how crucial sufficient home dialysis payments are to ensure patient modality choice and equitable access to home dialysis.

Key proposed changes to the Quality Incentive Program

In addition to recommending payment changes, the rule proposes modifications and additions to the ESRD QIP, which sets minimally acceptable patient outcome standards and mandates reporting on certain aspects of care. Under the QIP, facilities that do not meet the QIP's standards for quality measures receive a payment reduction of up to 2 percent.

Given the limited scientific evidence currently available regarding what comprises optimal care for patients on dialysis, the society has voiced reservations about some aspects of the QIP and is likely to do so again this year. ASN will also call attention to measures that are overly focused on processes—such as monitoring and collecting data—rather than on outcomes that reflect quality and value.

One new issue the policy board and task force will be assessing this year is the relationship between the QIP program and another new dialysis facility quality evaluation program CMS recently announced: the Five Star Rating System. The proposed rule does not discuss the Five Star system, although the program appears to have some similar goals to the QIP, including providing information for patients and their families to compare facilities' performance and quality of care. ASN and others will be seeking clarity on the Five Star program and its relationship to other programs, as well as assessing the new program in its own right.

CMS has hinted for several years that it would like to implement a Standardized Readmission Ratio (SRR) measure for dialysis facilities, and in this rule proposes adding the SRR in 2017. In concept, ASN strongly supports assessing hospital readmissions and believes such a measure would have great potential for improving patient care. But as with every aspect of quality measurement, the devil is in the details, and the society has numerous questions and concerns it believes must be addressed before the measure is finalized.

There are several challenges in methodology and other questionable aspects of the SRR measure that lack validity. One concern is defining the denominator as the number of discharges rather than by the total number of beneficiaries; this has the effect of allowing a single patient with repeated admissions to drive the entire performance of this metric. ASN also believes it is important that facilities have the opportunity to interact with patients before being held accountable for their readmissions.

"Unlike the proposed ESRD Seamless Care Organizations (ESCOs), which by design incentivize investment in elements such as hospital-based transition care coordinators to reduce readmission, dialysis facilities do not currently have such coordinators. Accordingly, if a discharged patient is readmitted prior to being seen at the dialysis facility, the facility would not have the opportunity to intervene to prevent the readmission," said ASN Quality Metrics Task Force Chair Daniel E. Weiner, MD. This is one of many changes ASN will be encouraging CMS to consider should it move forward with implementing what is currently a flawed measure.

Notably, the SRR measure—in its current form—was not supported by the members on the Technical Expert Panel (TEP) that CMS convened to contribute expertise to its development, nor has the measure been endorsed by the National Quality Forum (NQF). Adopting NQF-endorsed measures is CMS' stated preference, making its proposed adoption at this time unusual. The society is concerned that, ultimately, the TEP had little influence on or input into the measure's development. This is one of several examples the kidney community has recently seen suggesting that the overall TEP measure development process is not functioning as well as possible, a concern ASN is working to address with CMS.

One positive change is CMS' proposal to transition the anemia management measure (Hgb >12 g/dL) from a clinical measure to a reporting-only measure. ASN will commend CMS for this action in its comment letter. The society has advocated for removal of this unneeded clinical measure in the past for several reasons, including—as CMS acknowledged in the proposed rule—that the measure is "topped out," with virtually 100% of facilities achieving the measure standards. Keeping topped out measures in the program dilutes the effectiveness of the more meaningful measures in the calculation of overall performance scores, and ASN generally supports a shift toward a smaller number of important measures.

Notably, CMS cannot completely eliminate an anemia measure from the QIP at this time because the Medicare Improvements for Patients and Providers Act (MIPPA) statute mandates that the QIP include a measure of anemia management in the QIP. Because CMS eliminated the low-end anemia management measure (Hgb <10 g/dL) several years ago and has not implemented any additional anemia management measures, it must maintain the Hgb >12 g/dL as a reporting-only measure to remain compliant with the law.

For calendar year 2018, CMS also proposes implementing a standardized transfusion ratio (STrR) that would include Medicare patients who have been diagnosed with ESRD for at least 90 days, along with many other patient exclusions/caveats. ASN has long advocated that CMS monitor unintended consequences that adversely affect dialysis patients, including transfusion rates. The policy board and task force are assessing the details of the proposed measure and will provide recommendations in the ASN comment letter. Please visit the ASN Advocacy and Public Policy website (http://www.asn-online.org/policy/) for more information on the proposed rule and to read the society's final comment letter to CMS.

KIDNEY HEALTH INITIATIVE

Kidney Health Initiative Receives Second Round of Proposals

Nearing its two-year anniversary this September, the Kidney Health Initiative (KHI) continues to make advances toward fulfilling its mission of encouraging innovation and patient safety in kidney disease through its collaborative partnership between the FDA and the kidney community.

The Kidney Health Initiative held its Second Annual Stakeholders Meeting in June in Bethesda, MD. The annual meeting brought together its diverse membership from the kidney community, connecting members across different fields and allowing them to share ideas, discuss ongoing projects, collect feedback, and collaborate on new projects. Of the more than 100 U.S. and international attendees, nearly a third represented FDA and government agencies, a third were affiliated with industry, and a third represented patients and health-care professionals.

Mark McClellan, MD, PhD, provided his perspective during the opening session on the intersection between incentives and innovation in the context of the unique infrastructure that has evolved around the management of kidney disease in the United States. Dr. McClellan currently serves as the senior fellow and director of the Health Care Innovation and Value Initiative at the Brookings Institution, and his presentation drew from his wealth of experience in this area from his time as FDA Commissioner and CMS Administrator.

Following Dr. McClellan's presentation, small group breakout sessions allowed members to review current KHI projects and provide feedback to authors of project proposals in interactive and engaging presentations. In order to review the meeting's entire agenda please visit KHI's meeting page online at www.kidneyhealthinitiative.org.

As a member-driven initiative, KHI seeks to meet its mission and objectives through the completion of various projects proposed by members across all areas of the kidney community. KHI recently collected submissions from members for project ideas via an online web portal with its second project proposal submission cycle in June 2014. During the second cycle, KHI received the following 12 project proposals seeking endorsement from the KHI Board of Directors. The proposals reflect the diversity of KHI's membership and interests and also the huge potential to be able to make an impact on kidney disease through such projects.

- Advancing Technologies to Facilitate Remote Management of Patient Self-Care in Renal Replacement Therapy (RRT)
- Aligning Existing Voices | KHI Kidney Patient Voices Project
- Barrier to Clinical Trials—Increasing the Number of Nephrology Investigators to Facilitate the Formation of CKD Consortiums and Centers of Excellence in Clinical Research
- Design of Clinical Studies in Acute Kidney Injury
- Designing Patient-Centered Studies that Address Supportive Care for Frail Older Adults with Advanced Kidney Disease
- Educational Video to Increase Kidney Patient Participation in Clinical Studies
- Enhancing Quality of Life for Patients Undergoing Maintenance Dialysis: Exploring the Role of Patient-Reported Outcomes for Drug Approval
- Pragmatic Trials in Nephrology: Challenges and Opportunities
- Priorities for Drug Safety Evaluation Across the Spectrum of CKD
- Regulatory Policies and Positions Affecting Device Approval in the US: Tools to Assess the Process and Foster Device Development for Patients with Kidney Disease
- Unified Kidney Fact Sheet
- Vascular Access Data Collection

The KHI Board of Directors will meet later this summer to determine which proposals will be officially endorsed. Project workgroups will begin to form and meet in September 2014.

The web-based project portal provides KHI members with an opportunity to submit brief project proposals and also to discuss and refine submissions through this online forum. ASN members may submit project ideas for KHI by contacting the appropriate ASN Advisory Group. KHI has planned its third project proposal submission cycle for winter 2014/2015. To learn more about KHI's current projects, workgroup members, and proposals visit KHI online at www.kidneyhealthinitiative.org.

KHI will also continue to foster dialog among its members with an upcoming workshop at ASN Kidney Week in Philadelphia on November 11, 2014. The workshop will be presented by workgroup members of the KHI Pilot Project: Pharmacokinetics in Patients Receiving Continuous Renal Replacement Therapy, which finalized their recommendations earlier this year. The workshop will present and discuss the workgroup's recommendations. For more information about this topic, visit the KHI website at www.kidneyhealthinitiative.org or contact KHI staff at KHI@asn-online.org.

As KHI approaches its two-year anniversary, the Initiative looks forward to continued growth and interaction among its diverse membership in order to facilitate the passage of drugs, devices, and biologics into the kidney space. If interested in receiving more information about KHI or enrolling as a member, please contact the KHI staff at KHI@asn-online.org.

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Our Roots Go Deep

Hypertension Guidelines

The recently released American Society of Hypertension (ASH) and International Society of Hypertension Clinical Practice Guidelines for the Management of Hypertension sparked controversy in the kidney care community. Here, George Bakris, MD, FASN, analyzes the new guidelines. Bakris is director of the ASH Comprehensive Hypertension Center in the department of medicine at the University of Chicago School of Medicine.

ASN Kidney News *gratefully acknowledges the contributions of Edgar V. Lerma, MD, FASN, to this special feature.*

You have been actively involved with previous Joint National Committees (JNCs). Give us some background about the JNC and its evolution.

The JNC started in the early 1970s after a private donor gave a grant to the National Institutes of Health to help produce guidelines in hypertension. The aim was to help practicing physicians better manage patients' blood pressure (BP). The first guideline was published in 1977, and the last true JNC was the JNC7, published in 2003. When I say "true" JNC I mean that when a guideline document was produced, it was reviewed by many representatives of more than 45 different organizations, including the American Society of Nephrology, the National Kidney Foundation, the American Heart Association (AHA), the American Society of Hypertension (ASH), and many more.

The most recent JNC8, published in 2013, did not have that level of review; in fact, only about 25 or 30 people from the various societies reviewed the document. All the JNCs carefully selected topics of interest to clinicians and reviewed the published literature based on several criteria for the selection of articles. Multicenter outcome trials are preferred, but smaller studies, if relevant and well designed, are also reviewed. Individuals in the writing group have specific areas they cover. The group then meets to discuss the text and recommendations, and over time the JNC is born. JNC8 likewise had a panel that selected topics, but an independent evidence review company of epidemiologists and statisticians did the analyses. Grading was then done on the basis of criteria prespecified by the panel, and guidelines were then written. This process is similar to that for the National Institute for Health and Care Excellence (NICE).

What was the impetus that led the ASH and the International Society of Hypertension (ISH) to decide to publish their own *Clinical Practice Guidelines for the Management of Hypertension in the Community*?

The effort started out as a document to focus on management of hypertension in communities with low resources (like Haiti, where the initiative originated), and it evolved into the ASH/ISH guideline. I am not aware of the full details about how this happened, but the process was nothing like the JNCs. There was no formal evidence review, and the guidelines represent more of a narrative summary than a systematic review of the available data, interpretation of the data by a small group of authors, and then circulation for input from everyone. So it is more of a consensus report in the spirit of older AHA consensus reports, rather than a guideline document.

What are the most important highlights of the ASH/ISH *Clinical Practice Guidelines for the Management of Hypertension in the Community*?

The ASH/ISH Clinical Practice Guidelines reinforce many of the concepts already well established by JNC7 and focus more on African Americans than the JNC guidelines do. They are written in a fashion to review concepts and provide perspective. This is in contrast to JNC8, which is purely an evidence-based document that provides little to no narrative about perspective. The ASH/ISH guidelines provide an algorithm much like the JNC8 and are very consistent with data that support this approach.

How are the ASH/ISH Clinical Practice Guidelines different from JNC8 and hypertension guidelines produced by other organizations: NICE, International Society of Hypertension in Blacks, Kidney Disease: Improving Global Outcomes (KDIGO), European Society of Hypertension/European Society of Cardiology (ESH/ESC), Canadian Hypertension Education Program, and American Diabetes Association? What are the most important points of agreement or disagreement between the two sets of guidelines, such as target BP and initial BP? What are the reasons for these disparities?

First of all, a table in the JC8 document compares its recommendations with many other recent guidelines from around the world.

The JNC and NICE guidelines used a similar approach, as did the KDIGO, to a lesser extent. The ESH/ESC and ADA had a more traditional approach, although the ESH/ESC tried to grade the evidence. You must understand that if you want to "live by the evidence-based sword you must die by the sword." Thus, when the JNC8 quotes <150/90 mm Hg as a goal in individuals over 60 years of age, it is based on all the prospective clinical trial evidence and inclusion criteria, not on "opinion." It is one of only two A-level evidentiary statements in the JNC8. Moreover, all goals in the JNC8 are set as "ceilings," not "floors." This means that achieving a goal of <150/90 mm Hg is the absolute minimum expected, not the maximum. Clinical judgment is mandatory with all guidelines, such that a vibrant 75-year-old who does well with a BP of 130/70 mm Hg should not be allowed to let it rise to 150/90 mm Hg, which JNC8 states at the end of the document. Conversely, a 75-year-old who is symptomatic when the BP is 140/80 mm Hg should not be kept at this pressure.

The JNC8 and NICE, as well as KDIGO, simply made recommendations based on the purity of the data with much less interpretation than other guidelines. Does that make one right and the other wrong? No. The reader must be wise enough to understand the differences, and if you do not like the more literal guideline interpretations such as NICE and JNC8, then your argument is with the data from trials, not the writers. The good news is that the algorithms of the ASH/ISH and JNC8 are very similar, and they do serve well as an initial approach to BP management. The other good news is that the evidence review statements for JNC8 will be warehoused on the website of the *Journal of the American Medical Association*. However, there are no data to provide guidance for persons over 80 years of age and for other segments of the population. So these guidelines that are "evidence-based" are only as good as the foundation they are built on (i.e., the evidence).

In your guidelines, one of the headings focused on "Special Issues with Black Patients, African Ancestry." Tell us about this.

This is the largest ethnic group for whom hypertension is a major problem. This group also represents the largest number of people receiving dialysis today. The International Society of Hypertension in Blacks published an update of their guidelines a couple of years ago. These guidelines were, in part, evidence-based but included a lot of interpretation because of the relative lack of evidence on outcomes in this group. Thus, a focus on this group was considered necessary. You will note the scarcity in JNC8 of guidance for African Americans with diabetes, for example. While there was a paucity of recommendations for hypertension in African Americans in JNC8 there was also a paucity of data from which to derive recommendations.

Do you foresee more guidelines in the future?

Not in the foreseeable future. We have now been inundated with guidelines, and although they overlap in many ways, they are also perceived as contradictory in other ways. This is exemplified by a rebuttal paper published very recently by some of the JNC8 authors in the *Annals of Internal Medicine* regarding the goal of <150/90

mm Hg in older adults. Moreover, industry and NIH are unable to fund the large trials we have so far used to provide the evidence for such guidelines. I anticipate that the next guideline update will no longer come from the NIH but from the AHA/American College of Cardiology Foundation and respective collaborative groups like ASH, and that such an update will be at least 5 to 7 years away.

How will the new guidelines affect the way patients with hypertension are diagnosed and treated?

We hope there will be no impact on diagnosis, because nothing in any guideline has recommended a change in the method of diagnosis except for increasing patient empowerment in the use of home BP monitoring. We hope that treatment will be more focused and more aggressive initially, with the algorithms provided by both JNC8 and the ASH/ISH guidance. Physicians and health care professionals should understand that the goals for BP do not prevent caregivers from aiming for a lower BP if they think the patient can tolerate it, especially an elderly patient. I personally will not change my approach based on any of these guidances because I am already doing what they say, and I do not stop at BPs of 148/88 mm Hg in patients over 60 unless they can't tolerate the lower pressure.

We always look back to NHANES data for awareness of hypertension and its control and treatment. How do you think these guidelines will affect those numbers?

We hope the current level of BP goal achievement in the United States, i.e., 53% control rates, will not decrease as some fear. The control rates will look better in high-risk groups because the target blood pressure value has been raised. The key issue is what will happen to stroke rates. If health care providers understand that the goals for BP do not prevent caregivers from aiming for a lower BP if they think the patient can tolerate it, especially an elderly patient, stroke rates should not change. But if they allow people who have well-controlled pressure and who are tolerating medications to increase their BP to 150/90 mm Hg, the risk for and rate of stroke will probably increase.

Since the first few JNCs were released, what three or more things do you think practioners are now doing that were not done before, such as combination therapy, stepped care versus substitution, and stages of hypertension?

First, a clear focus on systolic BP in those over age 50 and diastolic BP in those under age 50 as a goal to reduce the risk of cardiovascular events. Second, using combinations of RAAS blockers with calcium channel blockers or thiazide diuretics as initial single-pill combinations for those whose BP is more than 20/10 mm Hg above their target BP. Third, the JNC8, like all previous and other current guidelines, focuses on lifestyle such as weight reduction and sodium intake more than before, to help with BP reduction. It is the first step in the JNC8 algorithm. Fourth, there is a greater understanding that more BP medications will not achieve BP control unless the patient commits to lifestyle modifications including sodium reduction and weight management.

With these new guidelines, are there any drug classes that you anticipate will be used more often? Less often?

I think there will be much less use of β-blockers as initial therapy unless a compelling cardiac condition exists. Likewise, I think that diuretics will be used less as initial therapy, given that all guidelines, including JNC8, suggest that either RAAS classified blockers, calcium channel blockers, or thiazide diuretics are appropriate first-line meds.

Publication of the VA NEPHRON D trial lent support to the previous findings of the ONTARGET and ALTITUDE trials in abandoning the previous use of combination ACE-I/ARBs. Do you think we've heard the last of these?

For the short term, yes. But keep in mind that with the exception of ONTARGET, all these trials were in advanced nephropathy. Moreover, in the VA-NEPHRON D trial there was a slight trend toward an increase in time to dialysis with the combination, albeit a post hoc analysis. With new better tolerated and more predictable potassium binding resins, which we hope will be on the market within the next year or so, something like the VA-NEPHRON could be repeated without the safety confounder of hyperkalemia to stop the trial prematurely and determine whether a difference really exists. But I doubt this will happen because of funding issues.

Practice Pointers

Venous Needle Dislodgement

By Beckie Michael, for the American Society of Nephrology Practicing Nephrologists Advisory Group

How frequent is venous needle dislodgement?

Venous needle dislodgement (VND) is an underreported life-threatening complication of hemodialysis. Its actual incidence is difficult to estimate. One report states that VND occurs more than 200 times daily in the United States and accounts for at least two deaths weekly. Five percent of patients report that VND occurred within the past 3 months, and 77% of dialysis nurses report seeing VND within the past 5 years. The Cleveland Clinic reported an incidence of 1 VND per 538 hemodialysis treatments before the initiation of a quality improvement project aimed at reducing VND, which resulted in a decrease in VND to 1 in 1750 treatments.

What are the consequences of VND?

VND can result in severe hemorrhage and can be fatal without rapid response. With blood pump speeds of 350 to 500 mL/min, VND can result in cardiovascular collapse within minutes. Slower leaks of blood around partially dislodged venous needles can also result in significant blood loss. VND often results in hospitalization, the need for transfusion, and increased requirements of erythropoietin and intravenous iron.

What can be done to prevent VND?

There are standardized procedures for anchoring the venous needle to the skin and dialysis lines to the patient. For catheters, a connector clip can be used to additionally secure the venous line to the venous limb of the catheter. The lower limit of the venous pressure alarm should be set as close to the actual venous pressure as possible. The patient's access site should be visible at all times.

What can be done to detect VND?

There is evidence that the use of the dialysis machine venous pressure alarm alone is not adequate to detect VND in many situations, including when a patient's venous pressure is very low (<25 mm Hg), when there is partial needle dislodgement, or when materials like clothing or blankets cover and obstruct the venous needle.

In 2010, a Veterans Administration patient safety alert recommended the use of an alarm to detect VND in high-risk patients. Patients who are restless or confused and those receiving dialysis outside the regular dialysis unit (in private or secluded rooms or by nocturnal hemodialysis) are at greatest risk. The Redsense dialysis alarm is a single-use fiberoptic blood sensor patch that is placed over the venous needle site. Blood detection will result in an audible and visual (flashing red light) alarm. A newer device, the WetAlert Wireless Wetness Detector, interacts with the 2008K@home hemodialysis machine. In addition to producing a visual and audible alarm, it automatically stops the blood pump and closes the venous line clamp when a blood leak is detected.

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Suggested Reading

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2. Morales M, Padilla-Kastenberg G. Venous needle dislodgement in dialysis clinic settings: a compilation of best practices and prevention. *Renal Business Today*. February 2013.
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Better Oral Health May Reduce Mortality Risk for Patients with End Stage Renal Disease

Better dental hygiene and oral health can lead to better overall outcomes for patients with end stage renal disease (ESRD). Researchers saw the effect regardless of the age at which patients initiated oral hygiene practices.

Poor oral health is a risk factor for cardiovascular and all-cause death among patients with chronic kidney disease (CKD). Compared to the general population, dialysis patients have more severe oral disease, and their uptake of dental health services is very low. But questions remain whether improving oral health would result in better outcomes.

No drug or other intervention appears to work very well to lower the elevated mortality risk of hemodialysis patients, so other interventions need to be examined, according to Giovanni Strippoli, MD, PhD, MPH, of the University of Bari, Italy, and Senior Vice President and Scientific Director of Diaverum, a global provider of renal services.

Therefore, Strippoli and colleagues undertook the prospective multinational ORAL Diseases in hemodialysis (ORAL-D) study involving 4320 consecutive adult hemodialysis patients recruited from randomly selected clinics in the Diaverum dialysis network in Europe and South America between July 2010 and February 2012. Patients had a mean age of 61.7 years, 58 percent were men, and 23 percent lacked teeth.

The study assessed the relationship between periodontal, dental, salivary, and mucosal health and mortality. At baseline, patients underwent a standardized oral examination and were surveyed about their dental health practices, other behavioral health risks, thirst, co-morbidities, and demographic factors.

Presenting the ORAL-D results at the the ERA-EDTA conference in Amsterdam, Strippoli reported that at a median follow-up of 22.1 months (12 months minimum), 650 participants died from any cause, and of those, 325 died from a cardiovascular event.

After adjusting for age, sex, income, smoking, cardiovascular disease, blood pressure, time on dialysis, and serum phosphorus level, the researchers saw a 27 percent increased risk of death (hazard ratio, HR = 1.27) among participants without teeth. Even worse, the risk of death in people with teeth (dentate) was elevated by 46 percent (HR = 1.46) for individuals with more than 12 decayed, missing, or filled teeth.

In the dentate population, oral hygiene practices were associated with a reduced risk of death by a statistically significant amount. Brushing teeth was associated with a 26 percent reduced risk of all-cause death, flossing 51 percent, changing a toothbrush at least every 3 months 21 percent, and spending 2 minutes or more on oral hygiene daily 19 percent. However, the age of starting dental care did not matter. The risk of death from cardiovascular causes followed a similar pattern. For people older than 60 years, the association between decayed, missing, and filled teeth and the risk of death was not as strong as for younger participants but was still statistically significant (31 percent greater; HR = 1.31).

The authors concluded that these results show an independent association between poor dental health and mortality for adult hemodialysis patients. Oral hygiene practices were associated with lower mortality.

A previously published meta-analysis by Strippoli and co-workers (*Nephrol Dial Transplant* 2014; 29: 364–375) comprising 11,340 adults with CKD in 88 studies supports the present findings. In that paper, they found that one in five people with stage 5D disease (therefore on dialysis) lacked any teeth, and 57 percent had periodontitis compared to 32 percent with less severe CKD. Among the stage 5D patients, 26 percent reported never brushing their teeth, only 11 percent flossed, 19 percent reported oral pain, and about half reported dry mouth.

Although a causal link between poor oral hygiene and all-cause or cardiovascular mortality cannot be drawn from observational data, and common pathways may be at play leading to oral problems and cardiovascular events, the authors did cite research showing that intensive periodontal treatment was associated with improved endothelial function. Furthermore, poor, painful, or absent dentition may be a factor in malnourishment.

Strippoli said the study findings strongly suggest that good dental care and dental hygiene should be urged for anyone with ESRD.

Novel Disease-Modifying Agent for Diabetic Nephropathy

A novel compound in development, emapticap pegol (emapticap; NOX-E36, Noxxon Pharma), a drug with anti-inflammatory properties, may be the first disease-modifying drug for the nephropathy in type 2 diabetes mellitus (T2DM). In a presentation at the European Renal Association—European Dialysis and Transplant Association conference in Amsterdam in June, researchers presented evidence that emapticap had positive effects on the kidney that persisted for several weeks after the drug was stopped.

Emapticap specifically binds and inhibits the pro-inflammatory chemokine CCL2 (also called monocyte chemotactic protein 1, MCP-1). Phase 1 studies showed it to be safe and well tolerated, and there were hints of renoprotective effects. These signals have now been followed up in a study involving 75 T2DM patients with albuminuria.

At the conference, Hermann Haller, MD, director of the department of nephrology and hypertension at the Hannover Medical School in Hannover, Germany, presented results of that randomized, double-blind, placebo-controlled, phase 2a study conducted at sites in five European countries.

Patients in the trial were on stable antidiabetic therapy and on drugs to block the renin-angiotensin system (e.g., ACE inhibitors or angiotensin receptor blockers). They had an albumin-to-creatinine ratio (ACR) >100 mg/g, an estimated glomerular filtration rate (eGFR) >25 mL/min/1.73 m^2, and a glycated hemoglobin (HbA_{1c}) between 6.0 percent and 10.5 percent. Patients received emapticap or placebo subcutaneously twice a week for 12 weeks and were followed for an additional 12 weeks without drug or placebo.

Haller reported that the drug reached pharmacologically active levels at the dose given and had the expected effect of reducing the number of monocytes bearing receptors for CCL2. Preclinical work had shown that this effect prevented the migration of inflammatory cells into the kidney, thereby preserving its structure and function, according to a news release from the company developing the drug.

Compared to placebo, emapticap reduced the mean ACR by 32 percent ($p = 0.014$) in the group of 49 patients deemed to be most relevant for future studies for this indication (i.e., censoring patients with kidney disease not from diabetes). Thirty-one percent of patients receiving the active drug had a 50 percent or greater reduction in ACR, compared to only 6 percent of patients receiving placebo. No differences were seen in blood pressure or eGFR between the emapticap and placebo groups, so the effect on ACR occurred independently of changes in blood pressure or eGFR and were thus presumably working through a different mechanism.

The patients on emapticap continued to receive benefit even after the drug was stopped and throughout the second 12-week (off-drug) period. The maximum decrease in ACR was seen 8 weeks after the last dose and was a mean 39 percent lower than for the placebo group ($p = 0.01$). At the end of the initial 12-week period, HbA_{1c} trended downward with emapticap compared to placebo (an absolute change from baseline of -0.32 percent vs. +0.06 percent, respectively; $p = 0.096$). This difference became statistically significant 4 weeks after the last dose ($p = 0.036$).

The researchers concluded that the drug is safe, well tolerated, and effective in reducing ACR and HbA_{1c} with prolonged administration in patients with T2DM and albuminuria. They noted that the renoprotective effect independent of blood pressure reduction distinguishes this compound from other drugs and is a novel approach.

Haller noted that the residual beneficial effect after the drug is stopped may indicate that emapticap ameliorates the underlying pathophysiology of the disease and "may hence be the first disease-modifying drug for this indication." The research group suggests further clinical studies to assess the potential of the drug to stave off end stage renal disease and cardiovascular events.

Aside from the renal effects, the reduction in HbA_{1c} suggests that emapticap also can benefit glycemic control.

In light of positive early results but then failure of some drugs in larger trials, confirmation of these phase 2 results is clearly warranted. Bardoxolone, a compound that reduced inflammation and oxidative stress, looked good in increasing eGFR among T2DM patients in phase 2b but failed in phase 3 because of higher cardiovascular mortality in the group receiving the drug.

Study Finds Better Survival With Cinacalcet Than Parathyroidectomy in CKD

Cinacalcet beats parathyroidectomy for improving survival of patients on chronic hemodialysis. The use of a vitamin D receptor activator (VDRA) along with cinacalcet produced additional survival benefit, researchers reported at the European Renal Association—European Dialysis and Transplant Association conference in Amsterdam in June.

These findings, from the 3-year, open-cohort, prospective Current management Of Secondary hyperparathyroidism — a Multicenter Observational Study (COSMOS), suggest that further, randomized, controlled trials should be conducted comparing medical vs. surgical treatment in the management of secondary hyperparathyroidism in chronic kidney disease (CKD).

It has been estimated that during the course of severe renal insufficiency more than 90 precent of patients on dialysis will develop some degree of secondary hyperparathyroidism. Increased serum parathyroid hormone (PTH) levels can lead to osteodystrophy, with attendant bone pain and fracture risk. In addition, vascular calcification can lead to cardiovascular events and death.

Parathyroidectomy can lower PTH levels. Alternatively, administration of active vitamin D can also normalize PTH levels, but serum calcium and phosphorus levels may increase significantly, again leading to vascular calcification. Cinacalcet (Sensipar, Amgen), by increasing the sensitivity of the calcium-sensing receptors in the parathyroid glands, inhibits excess production of PTH. Still, the question remained whether lowering serum PTH levels in itself was sufficient, or if the specific intervention that lowered the levels was important.

COSMOS gathered data from 227 hemodialysis centers in 20 European countries to evaluate methods of managing mineral and bone disorders in CKD. The study, conducted by Jorge Cannata-Andia, MD, head of the Bone and Mineral Research Unit at the Central University Hospital of Asturias and the University of Oviedo, Spain, and colleagues included 6251 hemodialysis patients—4285 at baseline and 1966 to replace those who died, received kidney transplants, switched to peritoneal dialysis, or were lost to follow-up.

The researchers used several approaches to analyzing the data, depending on whether patients were exposed to parathyroidectomy or to cinacalcet or not, with similar findings.

They found that cinacalcet use (independent of VDRAs) was associated with a 26 percent reduction in mortality risk (hazard ratio, 0.74). Combining cinacalcet with VDRAs lowered the risk by an additional 10 percent (hazard ratio, 0.65). Parathyroidectomy was not associated with a reduction in the risk of death.

The researchers concluded that the use of cinacalcet was superior to parathyroidectomy in terms of reducing the risk of mortality. Additional benefits were seen when VDRAs were added to cinacalcet.

Because observational studies, such as COSMOS, are subject to bias and confounding, the researchers advised performing randomized, controlled trials comparing cinacalcet and parathyroidectomy in this patient population.

Policy Update

KCP Legislation

By Rachel Meyer

Increasing kidney research. Improving our understanding of kidney failure in minority populations. Expanding access to kidney disease education. Addressing the nephrology workforce crisis. These important goals, and many other patient care and research objectives, are addressed in a new kidney bill that ASN strongly supports.

Congressional Kidney Caucus co-chair Rep. Tom Marino (R-PA)—himself a kidney patient—and longtime friend of the kidney community Rep. John Lewis (D-GA) jointly introduced the Chronic Kidney Disease Improvement in Research and Treatment Act (HR 4814) in June 2014. Since that time, ASN and other kidney community stakeholders have been advocating in support of the bill on Capitol Hill, highlighting how the more than 20 million Americans who have kidney disease and the nearly 600,000 who rely on dialysis stand to benefit from the provisions in this bill. In a letter urging their fellow members of Congress to support the bill, Reps. Marino and Lewis observed that "despite such a significant population, medical breakthroughs have been slow to materialize."

"ASN commends Rep. Marino and Rep. Lewis for making support for medical research such a key component of this bill," said ASN Public Policy Board chair Thomas H. Hostetter, MD. "This legislation helps call attention to the fact that kidney disease receives less federal research funding compared to other major chronic diseases, despite the fact that the federal government spends so much covering virtually all dialysis care. ASN believes the Government Accountability Report the bill requests will help the kidney community make the case for why greater funding is needed. And in calling for further investigation into why certain minority populations are at greater risk for kidney disease and how best to treat them, this bill helps advance a top ASN policy priority."

Beyond the kidney research provisions, the bill also addresses several access-to-care issues. For example, the bill would expand the types of nephrology health professionals who may provide the Medicare kidney disease education benefit and allow people who have later stage kidney disease but who are not yet on dialysis to receive the education benefit. These changes will make it possible for more patients to access this care as well as access it earlier in the course of their disease, slowing progression and helping them prepare for a smooth transition to dialysis or transplant.

The bill would also make changes to reimbursement for physicians who are caring for home dialysis patients and designate dialysis centers as approved telehealth sites. To address the lack of interest among trainees in nephrology as a career, the bill would provide loan repayment to nephrology health professionals who deliver care in underserved rural and urban areas. This incentive may help improve patient access and make it possible for more trainees to consider careers in nephrology.

For more details about the bill and how you can get involved to help ASN advocate for congressional support, please visit the ASN Advcocay and Public Policy webpage at http://www.asn-online.org/policy/.

Therapeutic Apheresis Medicine: Helpful Practical Advice at Your Fingertips

By Joseph Schwartz, Rasheed A. Balogun, and Marisa B. Marques

The practice of apheresis medicine, particularly in its use as therapy for specific conditions, is a burgeoning multidisciplinary field in which nephrologists in the United States and elsewhere are directly involved. Very often, a request comes from a different clinical service to use therapeutic apheresis as part of the treatment for specific conditions. At such times, the question "to treat or not to treat" arises because many factors need to be considered for a well-informed decision. Some of them include the following important questions: Is the disease or condition in the patient amenable to treatment with apheresis? If so, do the risks versus the benefits favor apheresis?

A great addition to the scholarly material available to help with this decision-making process has been coming from the American Society for Apheresis (ASFA) since 1986, the year of the publication of the first of a series of systematic reviews of therapeutic apheresis applications. These recommendations were revised every 7 years initially and, since 2007, every 3 years. The final product, also termed the Special Issue of the *Journal of Clinical Apheresis* or, more informally and more recently, the "ASFA guidelines," also addresses those dilemmas and helps clinicians make informed decisions. The past three special issues have been restructured to use an evidence-based approach.

The guidelines are composed of page-long fact sheets for each disease, including specific clinical presentations within each disease. At the top of the page, the role of therapeutic apheresis is categorized from I to IV (Table 1 and 2) and with the strength of the recommendation that is based on the quality of the most recent published evidence. The standardized format—a one-page fact sheet—allows for concise but comprehensive data to be presented, along with the references used to prepare the guidelines.

The sixth edition of the ASFA guidelines was published in the summer of 2013 (1). This current edition is the most comprehensive to date, encompassing 78 diseases or conditions, listed in alphabetic order from acute disseminated encephalomyelitis to Wilson disease. Table 2 includes all diagnoses considered to be category I indications for the various types of therapeutic apheresis. The ASFA guidelines have been used in the United States and beyond (translations to other languages exist) to help in the decision to treat or not to treat with therapeutic apheresis and, if so, how to appropriately perform the procedure (such as replacement fluid in therapeutic plasma exchange and number of plasma-volumes exchanged) and monitor the patient while protecting the patient's safety and ensuring the quality of the therapeutic apheresis care delivered.

Joseph Schwartz, MD, MPH, Rasheed A. Balogun, MD, and Marisa B. Marques, MD, write here as representatives of the American Society for Apheresis.

Reference

1. Schwartz J, et al. Guidelines on the use of therapeutic apheresis in clinical practice—evidence-based approach from the Writing Committee of the American Society for Apheresis: the sixth special issue. *J Clin Apher* 2013; 28:145–284.

Table 1
Definition of the ASFA categories

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment
III	Optimal role of apheresis therapy is not established; decision making should be individualized
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful; institutional review board approval is desirable if apheresis treatment is undertaken in these circumstances

Abbreviation: ASFA = American Society for Apheresis.

Table 2
Category I diseases for therapeutic apheresis according to the 2013 ASFA guidelines

Therapeutic plasma exchange
Thrombotic thrombocytopenic purpura, hyperviscosity syndrome, antiglomerular basement membrane antibody disease (Goodpasture syndrome), myasthenia gravis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multiple sclerosis (relapsing, progressive), PANDAS, Sydenham chorea, fulminant Wilson disease
Red blood cell exchange
Acute stroke in patients with sickle cell disease
Cytapheresis
Hyperleukocytosis with leukostasis
Extracorporeal photopheresis
Erythrodermic cutaneous T cell lymphoma, mycosis fungoides, Sezary syndrome
Selective adsorption
Familiar hypercholesterolemia

Abbreviations: ASFA = American Society for Apheresis; PANDAS = pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.

Fellows Corner

Programs Aim to Train Next Generation of Nephrologists

By Nishank Jain

There are several reasons why medical students and residents choose a career in nephrology. They include interest in physiology, interest in practicing a non–procedure-based subspecialty, and others (1). A key factor in their decisions is related to positive experiences during their nephrology rotations that can be accomplished only by enthusiastic and satisfied fellows and practicing nephrologists (1). Previous surveys have reported that the level of satisfaction experienced by nephrology fellows is related to their exposure to mentored clinical and scholarly activities during fellowship training (1).

With a trend toward declining interest in nephrology as a career (1, 2), the Mount Desert Island Biological Laboratory (MDIBL) in Maine aims to instill enthusiasm and thought-provoking training for medical students, residents, and nephrology fellows. It provides excellent mentoring in the basics of renal physiology and mechanistic approaches to the understanding of electrolyte disorders. The ASN TREKS (Tutored Research and Education for Kidney Scholars) includes the weeklong Origins of Renal Physiology workshop as part of its program (3).

The "Origins of Renal Physiology" course for residents, nephrology fellows, and faculty attempts to lay the groundwork for producing investigators and academic nephrologists by providing excellent hands-on experience in the basics of renal physiology and its history. Since its inception in 2008, the 1-week course has been conducted in mid-September at the MDIBL. It enrolls 30 trainees every year. From six modules—water homeostasis, salt homeostasis and secretion, collecting duct sodium balance, GFR, genetics, and proximal tubular function—each trainee registers in any three 1.5-day modules. During long workdays, each trainee performs classic experiments with the help of module-specific syllabi, collects data, and analyzes the data. Subsequently, data presentations are done by the trainees on the next afternoon in group laboratory meetings, with the intent that trainees learn from one another. Access to classic articles in nephrology, one or two guest lectures, and workshops on how to write manuscripts are provided during the week. Travel and housing are provided for the residents and fellows, who pay only a registration fee. The program is supported by an educational grant from the National Institute of Diabetes and Digestive and Kidney Diseases.

The ASN TREKS program supports medical students and graduate students pursuing a PhD to attend the course and become connected with a nephrologist-mentor who will interact with the student over the course of medical school training, graduate school, or postdoctoral fellowship. TREKS participants may attend ASN Kidney Week during the 3rd or 4th year of medical school or graduate school with travel support (as part of the ASN Kidney STARS program, formerly known as the ASN Program for Students and Residents, which is designed to help medical students develop long-term mentorships and to encourage careers in nephrology).

Fellowship clinical experience and general nephrology practice are heavily focused on short-term and long-term dialysis. Electrolyte disorders, which are intellectually stimulating, provide only a minor share of the daily workload in nephrology practice. In the process, knowledge of homeostasis and abnormalities may decline. Hands-on training in renal physiology and its history stimulates nephrologists and generates an outstanding grasp of the subject. It also provides teaching tools so that fellows and nephrologists can teach medical students and residents during case discussions and inpatient rounds. With the increasing demand for nephrologists and a declining interest in this subspecialty, it is essential to train next-generation nephrologists. The courses offered at the MDIBL attempt to instill enthusiasm and learning in students, residents, and fellows. In addition, they attempt to recruit medical students to commit to nephrology as a career. More information regarding the MDIBL and the national courses can be obtained at the following URLs:

- http://www.mdibl.org/
- http://www.mdibl.org/courses/Origins_of_Renal_Physiology_Renal_Fellows/114/.
- http://www.asn-online.org/education/training/students/kidney-treks.aspx

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3. Zeidel M, et al. A national course for renal fellows: the Origins of Renal Physiology. *J Am Soc Nephrol* 2008; 19:649–650.

Journal View

Kidney Donation Is Safe for Healthy Older Adults

For carefully selected adults aged 55 or older, the risks of cardiovascular disease (CVD) and mortality after living kidney donation are no higher than in healthy nondonors, according to a study in the *American Journal of Transplantation*.

The researchers identified 5152 patients who were 55 or older at the time of donor nephrectomy between 1996 and 2006. Of these, 3368 donors were matched to the same number of healthy nondonors drawn from the longitudinal Health and Retirement Study. The mean age was 59 years, 41 percent of donors were male, and 7 percent were African American.

At a median follow-up time of 7.8 years, mortality was not significantly different between groups: 4.9 deaths per 1000 person-years in living kidney donors and 5.6 per 1000 in nondonor control individuals. In an analysis of 1312 matched pairs with Medicare coverage, the groups were also similar on a combined outcome of time to death or CVD.

There was no increase in risk of diabetes among donors. In a subset analysis of pairs aged 60 or older, mortality was slightly lower for donors: hazard ratio 0.68.

Over the past 2 decades, living kidney donation by adults aged 55 or older has become more common. The new study is one of the first to focus on the safety outcomes for older kidney donors.

The results show similar risks of mortality and CVD for older living kidney donors and nondonor control individuals. The researchers conclude, "In the context of careful medical evaluation and selection, older donors should expect similar medium-term survival and risk of CVD compared to healthy members of the general population" [Reese P, et al. Mortality and cardiovascular disease among older live kidney donors. *Am J Transplant* July 9, 2014. doi: 10.1111/ajt.12822].

PCPs Support Kidney Disease Guidelines but Cite Barriers

Primary care physicians (PCPs) generally agree with clinical practice guidelines for chronic kidney disease (CKD), but they are less familiar with albuminuria, and they perceive barriers to its measurement, reports a study in *BMC Nephrology*.

An Internet survey evaluating knowledge, beliefs, attitudes, self-reported behavior, and perceived barriers to CKD care was sent to 12,000 PCPs in the United States. Of 848 physicians who opened the email, 165 responded (19.5 percent response rate). Eighty-eight percent of respondents spent more than half their time in clinical care, and 46 percent were in private practice.

Ninety-six percent of PCPs agreed that estimated GFR (eGFR) was useful in assessing kidney function. More than 70 percent believed that albuminuria testing would be useful. However, 20 percent said that a dipstick would not be helpful because of low reliability, and 30 percent thought that quantitative albuminuria testing would be burdensome to the patient.

In nondiabetic patients with hypertension, 75 percent of PCPs reported testing for albuminuria at an eGFR greater than 60 mL/min/1.73 m^2 and 91 percent at less than 60 mL/min/1.73 m^2. The respondents cited lack of effect on management, time limitations, and they perceived an absence of guidelines as barriers to albuminuria testing,

Although they broadly agreed with the definition of CKD, 30 percent of PCPs expressed concern about overdiagnosis in older patients at eGFR values in the stage 3a range. They agreed that angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers improved CKD outcomes, although agreement was lower at severe versus moderate albuminuria. About half of the PCPs stated that they were unfamiliar with CKD guidelines but were open to interventions aimed at improving CKD care.

Most CKD patients not receiving dialysis are treated by PCPs. This survey study suggests that most American PCPs agree with the current CKD guidelines. Efforts are needed to help PCPs become more familiar with CKD guidelines, to address barriers to albuminuria testing, and to help in targeting therapy with angiotensin-converting enzyme inhibitors and angotensin II receptor blockers [Abdel-Kader K, et al. Primary care physicians' familiarity, beliefs, and perceived barriers to practice guidelines in non-diabetic CKD: a survey study. *BMC Nephrol* 2014; 15:64].

Antibiotics Reduce Recurrence in Vesicoureteral Reflux

Prophylactic antibiotics lower the recurrence rate in children with vesicoureteral reflux (VUR) but do not affect the risk of renal scarring, concludes a randomized trial in the *New England Journal of Medicine*.

The multicenter trial included 607 children with VUR diagnosed after one or two episodes of urinary tract infection with fever. The median age was 12 months; 92 percent of the patients were girls.

One group received prophylactic trimethoprim-sulfamethoxazole, and the other group received placebo. The rates of febrile or symptomatic recurrences were compared at 2 years' follow-up. Secondary outcomes included renal scarring, treatment failure (recurrence, scarring, or both), and antimicrobial resistance.

Antibiotic prophylaxis reduced the rate of recurrent urinary tract infection: 12.9 percent versus 23.6 percent, relative risk 0.55. The hazard ratio for febrile or symptomatic recurrence was 0.50 in the antibiotic group, and this difference widened over time. The benefit was larger in children whose index infection was febrile and in those with baseline bladder and bowel dysfunction: hazard ratios 0.41 and 0.21, respectively.

The rates of renal scarring were similar between groups: 11.9 percent in those taking trimethoprim-sulfamethoxazole and 10.2 percent in those taking placebo. In 97 children with initial recurrence caused by *Escherichia coli*, isolates resistant to trimethoprim-sulfamethoxazole were found in 63 percent of the prophylaxis group versus 19 percent of the placebo group.

The new trial shows a significant reduction in recurrence with prophylactic trimethoprim-sulfamethoxazole. However, antibiotic treatment does not reduce the risk of renal scarring, and it increases the emergence of antibiotic-resistant bacteria. The authors discuss the implications for decisions about urinary tract imaging in children with VUR after febrile urinary tract infection [The RIVUR Trial Investigators: Antimicrobial prophylaxis for children with vesicoureteral reflux. *N Engl J Med* 2014; 370:2367–2376].

Smaller Declines in Kidney Function Still Predict ESRD and Death

Kidney function declines of less than a doubling of serum creatinine are common and are strong predictors of ESRD and mortality, according to a meta-analysis in the *Journal of the American Medical Association*.

The analysis included individual-level data on 1.7 million patients from 35 cohorts included in the CKD Prognosis Consortium, including repeated measurements of serum creatinine over 1 to 3 years. The 2-year percentage change in eGFR was analyzed as a predictor of all-cause mortality and ESRD, with adjustment for confounders and baseline eGFR. The analysis included a total of 12,344 ESRD events and 223,944 deaths.

Greater declines in eGFR carried larger increases in risk for both outcomes. For patients with a baseline eGFR less than 60 mL/min/1.73 m^2, the adjusted hazard ratio for ESRD was 32.1 with a 57 percent drop in eGFR versus 5.4 for a 30 percent reduction. However, the larger decline in eGFR occurred in just 0.79 percent of patients, whereas the smaller decline occurred in 6.9 percent.

The association was consistent across groups defined by length of baseline period, baseline eGFR level, patient age, diabetes status, or albuminuria. At a baseline eGFR of 35 mL/min/1.73 m^2, the adjusted 10-year risks of ESRD were 99 percent for patients with a 57 percent reduction in eGFR, 83 percent with a 40 percent reduction, 64 percent with a 30 percent reduction, and 18 percent with no change in eGFR. The risks of death were 77 percent, 60 percent, 50 percent, and 32 percent, respectively.

Doubling of serum creatinine—corresponding to a 57 percent reduction in eGFR—is typically regarded as a late event in CKD. The new study shows that lesser declines in kidney function are much more common but are still "strongly and consistently" associated with an increased risk of ESRD and death. The authors suggest that a 30 percent reduction in eGFR over 2 years might be a useful alternative end point in studies of CKD progression [Coresh J, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA* 2014; 311:2518–2531].

Harms of Glucose-Lowering Therapy Sometimes Outweigh Benefits

Especially in older patients, the burdens of intensive glucose-lowering treatment for type 2 diabetes—particularly with insulin—may exceed the benefits, suggests a study in *JAMA Internal Medicine*.

A Markov stimulation model was used to examine the impact of treatments to reduce hemoglobin A1c (HbA_{1c}) on diabetes complication rates and quality-adjusted life-years (QALYs), based on published data. The results suggested that treatment benefits varied substantially with patient age. Assuming a low treatment burden, treatments to lower $HbA1_c$ by 1 percentage point had a net benefit of 0.77 to 0.91 QALYs for patients receiving diagnoses of type 2 diabetes at age 45, compared with just 0.08 to 0.10 QALYs for those receiving diagnoses at age 75. At a higher treatment burden (3.7 lost days per year), the harms of HbA_{1c}-lowering therapy exceeded the benefits for 75-year-old patients.

Metformin, with relatively small treatment disutility, was beneficial across age groups: net benefit 1.2 QALYs in a 45-year-old patient and 0.148 QALYs in a 75-year-old patient. The absolute reduction in ESRD risk was nearly 10 times greater in a 45-year-old patient than in a 75-year-old patient: 0.065 versus 0.007.

In contrast, starting insulin in response to later increases in HbA_{1c} had a negative impact on QALYs in all age groups. The absolute reduction in ESRD achieved by starting insulin at age 55 was just 0.013.

The trend in type 2 diabetes treatment has been toward intensive glycemic control with lower HbA_{1c} targets. However, the benefits of treatment may take years to accrue, whereas the burdens and adverse effects begin much earlier.

The new study suggests that treatments to improve glycemic control are beneficial particularly for younger patients with type 2 diabetes. However, intensified treatment—especially adding insulin to metformin therapy—may be of little or no net benefit for older patients. "Thus, shared decision making, in which patient preferences are specifically elicited and considered, appears to be the best approach to making most decisions about glycemic management in patients with type 2 diabetes," the researchers write [Vijan S, et al. Effect of patients' risks and preferences on health gains with plasma glucose level lowering in type 2 diabetes mellitus. *JAMA Intern Med* June 30, 2014. doi:10.1001/jamainternmed.2014.2894].

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For some ESRD patients...

SWALLOWING PILLS IS NO JOKE

Switching to Phoslyra® (calcium acetate oral solution) may save them the struggle of swallowing over 3,000 phosphate binder (PB) pills a year.*

Phoslyra®
calcium acetate oral solution
667 mg per 5 mL

The Liquid Option

*Based on a mean of 8.4 ± 4.4 PB pills per day[1]

INDICATION:
Phoslyra is a phosphate binder indicated for the reduction of serum phosphorus in patients with end stage renal disease (ESRD). Phoslyra is administered orally with food.

IMPORTANT SAFETY INFORMATION:

- **Phoslyra is contraindicated in patients with hypercalcemia.**
- **Patients should have serum calcium levels closely monitored and their dose of Phoslyra adjusted or terminated to bring levels to normal.** No other calcium supplements should be given concurrently with Phoslyra.
- Phoslyra may decrease the bioavailability of tetracyclines or fluoroquinolones.
- There are no empirical data on avoiding drug interactions between calcium acetate or Phoslyra and most concomitant drugs. When administering an oral medication with Phoslyra where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, administer the drug 1 hour before or 3 hours after Phoslyra or calcium acetate. Monitor blood levels of the concomitant drugs that have a narrow therapeutic range.
- The most common (>10%) adverse reactions experienced with Phoslyra are hypercalcemia, nausea, and diarrhea. Of the observed drug-related adverse reactions, diarrhea (5/38, 13.2%) was more common with Phoslyra than with a solid formulation calcium acetate.
- Phoslyra may cause diarrhea with nutritional supplements that contain maltitol.

For additional important safety information, please see the brief Prescribing Information on this page.

Reference: 1. Sussman E, Mullon C, Ginsberg N, et al. Amount of fluid ingested with phosphate binders in hemodialysis-dependent CKD patients. Poster and abstract presented at National Kidney Foundation 2010 Spring Clinical Meeting, April 15-17, 2010, Orlando, Fla.

Manufactured for and distributed by: Fresenius Medical Care NA, Waltham, MA 02451. For more information on Phoslyra, please contact Fresenius Medical Care NA at 800-323-5188.

PN 102352-01 Rev. A 04/2014

Brief Summary: Consult full package insert for complete Prescribing Information.

INDICATIONS AND USAGE: Phoslyra® (calcium acetate oral solution 667 mg per 5 mL) is a phosphate binder indicated to reduce serum phosphorus in patients with end stage renal disease (ESRD). Management of elevated serum phosphorus levels usually includes all of the following: reduction in dietary intake of phosphate, removal of phosphate by dialysis, and inhibition of intestinal phosphate absorption with phosphate binders.

DOSAGE AND ADMINISTRATION: The recommended initial dose of Phoslyra for the adult dialysis patient is 10 mL with each meal. Increase the dose gradually to lower serum phosphorus levels to the target range, as long as hypercalcemia does not develop. Titrate the dose every 2 to 3 weeks until an acceptable serum phosphorus level is reached. Most patients require 15–20 mL with each meal.

CONTRAINDICATIONS: Patients with hypercalcemia.

WARNINGS AND PRECAUTIONS:

Hypercalcemia. Patients with end stage renal disease may develop hypercalcemia when treated with calcium, including calcium acetate (Phoslyra). Avoid the concurrent use of calcium supplements, including calcium-based nonprescription antacids, with Phoslyra. An overdose of Phoslyra may lead to progressive hypercalcemia, which may require emergency measures. Therefore, early in the treatment phase during the dosage adjustment period, monitor serum calcium levels twice weekly. Should hypercalcemia develop, reduce the Phoslyra dosage or discontinue the treatment, depending on the severity of hypercalcemia. More severe hypercalcemia (Ca >12 mg/dL) is associated with confusion, delirium, stupor and coma. Severe hypercalcemia can be treated by acute hemodialysis and discontinuing Phoslyra therapy. Mild hypercalcemia (10.5 to 11.9 mg/dL) may be asymptomatic or manifest as constipation, anorexia, nausea, and vomiting. Mild hypercalcemia is usually controlled by reducing the Phoslyra dose or temporarily discontinuing therapy. Decreasing or discontinuing Vitamin D therapy is recommended as well. Chronic hypercalcemia may lead to vascular calcification and other soft-tissue calcification. Radiographic evaluation of suspected anatomical regions may be helpful in early detection of soft tissue calcification. The long-term effect of Phoslyra on the progression of vascular or soft tissue calcification has not been determined.

Hypercalcemia (>11 mg/dL) was reported in 16% of patients in a 3-month study of a solid dose formulation of calcium acetate; all cases resolved upon lowering the dose or discontinuing treatment. Maintain the serum calcium-phosphorus product (Ca X P) below 55 mg^2/dL^2.

Concomitant Use with Medications. Hypercalcemia may aggravate digitalis toxicity. Phoslyra contains maltitol (1 g per 5 mL) and may induce a laxative effect, especially if taken with other products containing maltitol.

ADVERSE REACTIONS: No clinical trials have been performed with Phoslyra in the intended population. Because the dose and active ingredients of Phoslyra are equivalent to that of the calcium acetate gelcaps or tablets, the scope of the adverse reactions is anticipated to be similar.

Hypercalcemia is discussed elsewhere *[see Warnings and Precautions]*.

Clinical Trial 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 clinical practice.

In clinical studies, calcium acetate has been generally well tolerated.

The solid dose formulation of calcium acetate was studied in a 3-month, open-label, non-randomized study of 98 enrolled ESRD hemodialysis patients and in a two week double-blind, placebo-controlled, cross-over study with 69 enrolled ESRD hemodialysis patients. Adverse reactions (>2% on treatment) from these trials are presented in Table 1.

Table 1: Adverse Reactions in Patients with End-Stage Renal Disease Undergoing Hemodialysis

	Total adverse reactions reported for calcium acetate n=167	3-mo, open-label study of calcium acetate n=98	Double-blind, placebo-controlled, cross-over study of calcium acetate n=69	
			Calcium acetate	Placebo
Preferred Term	n (%)	n (%)	n (%)	n (%)
Nausea	6 (3.6)	6 (6.1)	0 (0.0)	0 (0.0)
Vomiting	4 (2.4)	4 (4.1)	0 (0.0)	0 (0.0)
Hypercalcemia	21 (12.6)	16 (16.3)	5 (7.2)	0 (0.0)

Calcium acetate oral solution was studied in a randomized, controlled, 3-arm, open label, cross-over, single-dose study comparing calcium acetate oral solution to a solid formulation in healthy volunteers on a controlled diet. Of the observed drug-related adverse reactions, diarrhea (5/38, 13.2%) was more common with the oral solution.

Postmarketing Experience. The following additional adverse reactions have been identified during post-approval of calcium acetate: dizziness, edema, and weakness.

DRUG INTERACTIONS: The drug interaction profile of Phoslyra is characterized by the potential of calcium to bind to drugs with anionic functions (e.g., carboxyl, carbonyl, and hydroxyl groups). Phoslyra may decrease the bioavailability of tetracyclines or fluoroquinolones via this mechanism.

There are no empirical data on avoiding drug interactions between calcium acetate or Phoslyra and most concomitant drugs. When administering an oral medication with Phoslyra where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, administer the drug one hour before or three hours after Phoslyra or calcium acetate. Monitor blood levels of the concomitant drugs that have a narrow therapeutic range. 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 with all forms of calcium acetate.

Ciprofloxacin. In a study of 15 healthy subjects, a co-administered single dose of 4 calcium acetate tablets (approximately 2.7 g) decreased the bioavailability of ciprofloxacin by approximately 50%.

USE IN SPECIFIC POPULATIONS

Pregnancy: Category C. Phoslyra contains calcium acetate. Animal reproduction studies have not been conducted with Phoslyra, and there are no adequate and well controlled studies of Phoslyra use in pregnant women. Patients with end stage renal disease may develop hypercalcemia with calcium acetate treatment *[see Warnings and Precautions]*. Maintenance of normal serum calcium levels is important for maternal and fetal well being. Hypercalcemia during pregnancy may increase the risk for maternal and neonatal complications such as stillbirth, preterm delivery, and neonatal hypocalcemia and hypoparathyroidism. Phoslyra treatment, as recommended, is not expected to harm a fetus if maternal calcium levels are properly monitored during and following treatment.

Labor and Delivery. The effects of Phoslyra on labor and delivery are unknown.

Nursing Mothers. Phoslyra contains calcium acetate and is excreted in human milk. Human milk feeding by a mother receiving Phoslyra is not expected to harm an infant, provided maternal serum calcium levels are appropriately monitored.

Pediatric Use. Safety and effectiveness of Phoslyra in pediatric patients have not been established.

Geriatric Use. Clinical studies of calcium acetate 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, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

OVERDOSAGE: Administration of Phoslyra in excess of the appropriate daily dosage may result in hypercalcemia *[see Warnings and Precautions]*.

HOW SUPPLIED/STORAGE AND HANDLING: Phoslyra for oral administration is a clear solution containing 667 mg calcium acetate per 5 mL. Phoslyra is supplied in a 473 mL (16 oz) amber-colored, multiple-dose bottle, packaged with a marked dosing cup. Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. The shelf life is 24 months.

PATIENT COUNSELING INFORMATION: Inform patients to take Phoslyra with meals, adhere to their prescribed diets, and avoid the use of calcium supplements including nonprescription antacids. Inform patients about the symptoms of hypercalcemia *[see Warnings and Precautions and Adverse Reactions]*.

Advise patients who are taking an oral medication where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy to take the drug one hour before or three hours after Phoslyra.

Manufactured for:
Fresenius Medical Care North America
Waltham, MA 02451 1-800-323-5188

Manufactured by:
Lyne Laboratories
Brockton, MA 02301

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