ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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FDA Could Approve First Biosimilar Drug for Dialysis this Year

By Eric Seaborg

The US Food and Drug Administration (FDA) could approve the first biosimilar drug for use in dialysis patients later this year, a prospect that could shake up the market with an alternative to Amgen's dominant anemia biologic drug Epogen (epoetin alfa) that has been used in Europe for several years.

Biosimilars are essentially the generic versions of biologic drugs, which are compounds that are made by or derived from living organisms rather than manufactured like most drugs. Because biologics—which include compounds such as the erythropoiesis-stimulating agent (ESA) epoetin, monoclonal antibodies, interferons, and human insulin—are derived using organic processes, they cannot be duplicated exactly. They show much more heterogeneity, batch-to-batch variability, and other variations compared with generic drugs, which merely require replication of the chemical formula in a controlled manufacturing process.

As patents on the first biologics began to expire, enabling companies to consider the creation of drugs based on similar principles to compete with them, the need arose for a pathway to approve these biosimilars. Because their equivalence is not as obvious as that of a generic drug, regulators wrestled with the question of what standards would be reasonable to meet without going through the approval process for a brand new drug. The European Union put such a pathway in place in 2005.

In the US, a provision of the Affordable Care Act called the Biologics Price Competition and Innovation Act of 2009 empowered the FDA to implement an abbreviated regulatory approval process for biosimilars. A manufacturer must provide clinical studies showing that a product has no meaningful differences in terms of safety, purity, and potency in comparison to a "reference product"—a specific FDA-approved biologic.

After several years of working out the details, the FDA approved its first biosimilar drug in March—Sandoz's Zarxio (filgrastim-sndz), a biosimilar to Amgen's cancer drug Neupogen (filgrastim). The biosimilar widely considered to be next in the pipeline for approval is Hospira's epoetin zeta, a competitor to Amgen's epoetin alfa, used to treat anemia in patients with chronic kidney disease (CKD).

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ICD-10 Coding Switch: Short-term Headaches; Long-Term Benefits

On October 1, 2015, US healthcare providers will transition to the tenth version of ICD-10, the World Health Organization (WHO) disease classification system. Approved by WHO in 1990, ICD-10 is now used by more than 115 countries to record morbidity and mortality statistics, and more than 20 countries incorporate ICD-10 into their reimbursement processes. The US version, modified by the National Center for Health Statistics (NCHS) and the Centers for Medicare and Medicaid Services (CMS), includes ICD-10 Clinical Modification (ICD-10-CM), comprising 68,000 codes for use in clinical settings, and the ICD-10 Procedure Coding System (ICD-10-PCS), comprising an additional 75,000 procedure codes.

Methods of disease classification developed in England and France in the 17th and 18th centuries remain the foundation for systems used today to classify morbidity and mortality (1). The United States adopted the World

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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

IMPORTANT SAFETY INFORMATION

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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For more information please visit SAMSCA.com

Otsuka
Otsuka America Pharmaceutical, Inc.

June 2014

07US14EBP2751

SAMSCA® (tolvaptan) tablets for oral use

Brief Summary of Prescribing Information. Please see Full Prescribing Information for complete product information.

WARNING: INITIATE AND RE-INITIATE IN A HOSPITAL AND MONITOR SERUM SODIUM

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.

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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Biosimilar Drug

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A dominant drug

"Epoetin alfa is used in a majority of patients with dialysis-dependent CKD and in many individuals with non-dialysis-dependent CKD, and its high cost is a significant proportion of the total expense of treating patients with CKD," Steven Fishbane, MD, and Hitesh H. Shah, MD, wrote in an article, "The Emerging Role of Biosimilar Epoetins in Nephrology in the United States," in the *American Journal of Kidney Disease*. Epoetin alfa so dominates the market that it is Medicare's single largest drug expenditure, some $2 billion in 2010.

The five-year head start in Europe allows US healthcare providers to benefit from the European experience. "Biosimilar epoetin has been used in Europe since 2007, and a wealth of data has been collected. These studies and reports indicate that the efficacy and safety profiles of biosimilar epoetin are similar to those of originator epoetin alfa," Fishbane and Shaw said. And many studies have found significant cost savings from the use of biosimilars, similar to the use of generics compared with brand-name drugs.

How readily the US medical market will accept biosimilars remains to be seen. Many specialties tend to be conservative and slow to replace tried-and-true therapies, but the special circumstances of the dialysis market could make it more open to change, according to a study by the Marwood Group, a healthcare policy consulting firm. (ASN is a client of the Marwood Group and receives healthcare advisory services.) Marwood researchers conducted in-depth interviews with decision-makers at dialysis clinics to gauge their attitudes about biosimilars.

"Marwood believes that physicians will generally take a cautious approach to switching patients over from branded products to biosimilars," the report says. "However, in the case of erythropoiesis-stimulating agents, the bundled payment methodology for dialysis clinics has the potential to drive a more rapid adoption. Dialysis is one of the few areas of therapy where care is reimbursed at a bundled rate, which in this case includes the cost of anemia drugs such as Epogen. As a result, those in the business of running dialysis clinics are aware of the fixed payments they receive from Medicare and work to maximize quality of care while also likely trying to maximize profit. The more they can lower their cost to deliver care, the more likely they will increase their margins in each dialysis treatment."

"A lot of clinics are facing economic pressure," study author Stephen Williams, PhD, told *Kidney News*. "They see this as a good way to save some money for a product that is essentially almost identical to the branded product."

In their *AJKD* article, Fishbane and Shah said: "Availability of biosimilars in the United States is predicted to significantly reduce the cost of biologics and increase their availability, as has been the case in Europe, where cost analyses have reported substantial economic benefits."

Epoetin zeta

Hospira launched epoetin zeta under the brand name Retacrit in Europe in 2008 and in Australia in 2011, and the company has several other biosimilars in these markets. "Hospira has delivered more than 5 million doses of biosimilars to patients in Europe and Australia over the past five years, with no concerning reports of unusual or unexpected adverse events," according to the company's website. Nothing in the European experience indicates that there will be a problem in getting the epoetin zeta approved in the US.

Hospira presented a pair of randomized clinical studies at the National Kidney Foundation spring meeting that evaluated the pharmacokinetic and pharmacodynamic equivalence of epoetin zeta with Amgen's Epogen reference product in healthy volunteers. Both studies were consistent with a finding of biosimilarity between the products, according to a Hospira press release.

The FDA's goal is to complete its review of most biosimilar applications within 10 months of acceptance of the filing, a standard it met with approving Sandoz's Zarxio. Hospira submitted its epoetin zeta application in December 2014, so it could receive approval later this year.

Sandoz also has an Epogen biosimilar in development. It has been on the market in Europe for several years under the brand name Binocrit and has generated more than 160,000 patient-years in clinical experience. According to the company, Binocrit is the leading epoetin biosimilar in Europe. It has been in phase 3 clinical trials for some time, but Sandoz has not as yet filed for approval with the FDA.

Legal issues could cause delays

Legal issues surrounding expiring patents could delay a biosimilar's introduction into the market long after its approval by the FDA, said Kim Vukhac, who also worked on the Marwood Group study. Although the FDA has approved Sandoz's Neupogen-equivalent, and it is available in more than 60 countries worldwide, patent litigation has evidently prevented its US launch.

An established process governs the introduction of generic versions of brand name drugs. Brand name manufacturers must publish the patents protecting their drugs, so it is easy to know when the patents related to a drug expire. But no such directory exists for biologics. A company working to introduce a biosimilar is supposed to work with the company that makes the reference drug in a process that has come to be called the "patent dance," Vukhac said.

"It is a series of steps, a back and forth process, where the biosimilar company submits information to the reference brand company, and they are supposed

to work out what patents they will be litigating," she said. But Sandoz decided that it is not going to follow this patent dance for its newly approved biosimilar to Neupogen. The drug is not launching because Amgen and Sandoz are in court arguing over whether Sandoz needs to follow the patent dance. The two companies "are not even litigating at this point actual the patents, they are litigating how to litigate," Vukhac said.

Because these are the first products setting precedents for what could turn out to be a complicated legal process, even if an Epogen biosimilar is approved soon, "it is very possible we don't see a launch," Vukhac said.

"If there are patents still in existence around Epogen that Amgen decides to try to enforce, that could obviously delay things," Williams added. "It is not always easy to figure out what patents are out there, and it is different from the small molecule drugs, where you essentially know what [the patents] are because companies have to list them. In this case you don't actually have to list them, so finding them is more difficult than it might seem."

Another potential stumbling block that apparently will not affect clinics' adoption of a biosimilar is the experience with the failed anemia drug, Omontys (peginesatide). The FDA approved Omontys to treat anemia in adult dialysis patients with CKD in 2012. The drug offered an alternative to Epogen for less than a year. The manufacturers recalled all lots of the drug because some patients had severe hypersensitivity reactions, including anaphylaxis, that resulted in some deaths.

Dialysis clinic leaders indicated to the Marwood researchers that the Omontys experience would not affect their attitude toward biosimilars, perhaps because Omontys was a synthetic peptide, not a biologic drug or a biosimilar. "They saw it as an unfortunate incident specific to that product, not an issue that should be extrapolated to other products," Vukhac said.

History of use

Clinic leaders appear more likely to look to the European experience. "There is a history of successful use of Epogen-like products outside the US in sophisticated healthcare markets," Williams said. "I think that is helpful to the way that people think about these things. The products that are coming into the US are essentially the same ones that they are using in Europe today. It is the same companies, and the same processes that they are using to make these biosimilars, so it is not like we are totally starting from scratch here with the Epogen-like products."

Vukhac added that doctors are often seen as resistant to change, but the representatives of dialysis clinics interviewed indicated that they are open to switching. "They change their protocols fairly often, so they are pretty adaptive, which may be different from other specialties," she said.

How fast a biosimilar might penetrate the market is another open question. The Marwood report says: "According to SEC filings, DaVita has a contract with Amgen which runs through the end of 2018 stipulating that it will use Amgen's product for 90% of its ESA needs. This represents approximately one-third of the dialysis market. Fresenius is not bound by a similar contract, but is likely to take a measured approach as it has done previously with Omontys and most recently Mircera, Roche's pegylated ESA."

The report postulates that small- and medium-sized dialysis organizations will be the most receptive to cost savings that could accrue from biosimilar ESAs. "Smaller clinics have been under quite a bit of financial pressure. There have been cuts to the bundle over the last few years, so I think that finding ways to manage those cuts becomes top of mind," Williams said.

Dialysis clinics will no doubt welcome the availability of alternative drugs and suppliers that address one of their major costs, and while many questions remain, it appears to be only a matter of time until alternatives are available.

ICD-10 Coding Switch

Continued from page 1

Health Organization (WHO) Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death in 1948. The ninth version of this manual (ICD-9) was approved by WHO in 1975, and a version modified for the American hospital system was adopted in 1979. In the US, providers use Current Procedural Terminology (CPT) codes, updated yearly by the American Medical Association, to document and bill for specific medical procedures and services. ICD-9 disease classifications began to be incorporated into claims processing in the 1980s.

Why switch?

Since the adoption of ICD-9 in 1979, an explosion of new technologies, new procedures, and new quality measures has produced more detail than can be supported by the current system and codes. Moreover, today's healthcare is global, and it is becoming increasingly difficult to share data critical to public health and research when classification systems are out of sync. According to the American Health Information Management System, ICD-9 "can't take healthcare into the future" (2).

Many experts speculate that the increased specificity of ICD-10 codes will reduce the need for repetitive exchanges between providers and insurance companies regarding claims, and ultimately reduce the incidence of rejected claims. In addition, large and small healthcare providers may be able to use the increased specificity such as the coding for underlying causes and co-morbidities, to improve patient outcomes and better allocate internal resources.

No pain, no gain?

Success of transitions to ICD-10 will depend on many organizations, not just providers: electronic health record (EHR) vendors, insurance companies, and others must also convert their systems. Worst-case scenarios for physician practices during the transition include slowed productivity, higher percentages of rejected claims, and short-term increases in unbilled receivables.

To support the transition, on June 6, 2015, CMS and AMA issued a joint statement highlighting efforts to help physicians make the switch (http://cms.gov/Medicare/Coding/ICD10/Downloads/AMA-CMS-press-release-letterhead-07-05-15.pdf). CMS and AMA will provide educational support before the transition; to address questions post-transition, CMS will set up a communications center and support an ICD-10 ombudsman, and for 12 months post-transition, CMS will allow flexibility in claims and quality reporting.

Many of the new codes relate to the musculoskeletal system, with significant expansions in coding fractures, so some areas of practice will experience more change than others. Nephrology is not anticipating the same level of change as orthopedics, but all coders, physicians, and insurance companies must learn the new chapter organization, new codes, and adapt to providing more, and different kinds of, documentation. Combination codes that include acuity or severity will impact nephrology coding, especially chronic kidney disease (CKD). Diseases closely associated with kidney disease, such as diabetes and hypertension, will add to the learning curve for kidney physicians and staff. Several of the resources listed below focus on the impact of the conversion to ICD-10 on nephrology.

Within and outside the clinic setting, the conversion to ICD-10 may require efforts not yet fully anticipated. The General Equivalence Mappings (GEM) that support the transition from ICD-9 coding to ICD-10 coding in the clinic and hospital settings may not provide comparability ratios for tracking longitudinal data (3). New ICD-10 codes must be incorporated into reporting of quality measures: for example, each AHRQ quality indicator technical specification with ICD-9 CM codes must be converted to ICD-10 CM/PCS codes. After October 1, challenges may arise when ICD-10 codes cannot be used: for instance, in the US, workers' compensation and auto insurance claims are not required to incorporate ICD 10 coding.

While the headaches are predictable, the increased precision of these classifications, the improved integration with electronic health records, and the ability to convey more detailed data about patient outcomes, may prove great aids to nephrologists and others in their ongoing efforts to evolve and improve patient care.

Resources

- AMA Support for ICD 10 Transition: http://www.ama-assn.org/ama/ama-wire/blog/ICD-10_Monthly_Primer/1
- ICD-10 Myths and Facts http://www.cms.gov/Medicare/Coding/ICD10/downloads/icd-10mythsandfacts.pdf
- CMS: GEMS FAQs http://www.cms.gov/Medicare/Coding/ICD10/downloads/gems-crosswalksbasicfaq.pdf
- CMS: 2015 ICD-10 CM and GEMS http://www.cms.gov/Medicare/Coding/ICD10/2015-ICD-10-CM-and-GEMs.html
- CMS: 2015 ICD-10 PCS and GEMS http://www.cms.gov/Medicare/Coding/ICD10/2015-ICD-10-PCS-and-GEMs.html
- Road to 10: The Small Physician Practice's Route to ICD-10 (CMS) http://www.roadto10.org/
- Top 20 Nephrology ICD-9 to ICD-10 Codes http://www.pulseinc.com/wp-content/uploads/2013/10/Nephrology_ICD10Conversion.pdf
- ICD 10 Crosswalk for Nephrology http://nephrologypracticesolutions.com/icd-10-crosswalk
- How to document and code for hypertensive diseases in ICD 10 http://www.aafp.org/fpm/2014/0300/p5.html (includes information specific to hypertension and CKD)
- American Association of Professional Coders (AAPC) Code Translator https://www.aapc.com/icd-10/codes/
- ICD 10 Conversion and Mapping Tutorial https://www.aapc.com/icd-10/conversion-mapping.aspx
- Members of the Renal Physicians Association (RPA) may access nephrology-specific ICD 10 resources via the RPA website: http://www.renalmd.org/Coding-and-Billing/.

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3. Projected Impact of the ICD-10-CM/PCS Conversion on Longitudinal Data and the Joint Commission Core Measures http://perspectives.ahima.org/projected-impact-of-the-icd-10-cmpcs-conversion-on-longitudinal-data-and-the-joint-commission-core-measures/#.VZLK__lViko

Policy Update

2016 Federal Budget Process Breaks Down

By Grant Olan

The clock is running out for the US Congress to pass a federal budget for 2016 before the new fiscal year begins on October 1. Confidence is low that Congress will meet the deadline. Many in Washington predict Congress will keep funding the government at last year's funding levels until it can pass a full-year budget. But if Congress fails to achieve either a new budget for 2016 or agreement to keep government operating at 2015 funding levels, essential government services will shut down.

The last shutdown in 2013 lasted 16 days. Non-mandatory federal programs funded by Congress through the annual appropriations process such as medical research were affected. The National Institutes of Health (NIH), for instance, was unable to fund new grants and contracts during that time.

A major sticking point for many Democrats are the budget caps Congress passed in 2011 to curb the federal deficit. Democrats are refusing to support appropriation bills unless there is a broad agreement to raise the caps—and allow more spending—for both defense and non-defense discretionary (non-mandatory) programs.

As a result of the caps and other federal austerity measures, NIH has lost nearly 25% of its purchasing power since 2003. During the same time, China and other countries have been ramping up their investments in research. The consequences of the funding shortfall are apparent as grant application success rates reach an all-time low and as US scientists move oversees or leave the research field altogether.

NIH Director Francis Collins, MD, PhD, provided alarming testimony before the US House of Representative in March about the impact on student interest in research. "This is the issue that wakes me up at night when I try to contemplate the future of where biomedical research can go in the United States," Collins said. "They are finding themselves in a situation that is the least supportive of that vision in 50 years. They look ahead of them and see the more senior scientists struggling to keep their labs going and suffering rejection after rejection of grants that would have previously been supported. And they wonder, 'Do we really want to sign up for that?' And many of them, regrettably, are making the decision to walk away."

Despite the current fiscal climate, bipartisan support for increasing NIH's budget has swelled.The proposed 2016 budgets in the House and Senate both include increases for NIH. The House and Senate bills also provide the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) with increases of $22 million and $76 million, respectively.

Due to the budget cap limits on the total dollar amount Congress can spend on discretionary programs, the NIH increases would come at the expense of other public health and research programs many members of Congress who support NIH also value. The House and Senate bills cut or eliminate funding for the Agency for Healthcare Research and Quality (AHRQ) (the only federal agency that funds health services research), Centers for Disease Control and Prevention (CDC), and Health Resources and Services Administration (HRSA). The House bill also bans patient-centered research.

ASN is working with the Coalition for Health Funding and other partners in protesting these proposed tradeoffs, highlighting the importance of the entire research continuum, advocating to increase the budget caps, and building support for additional investments.

"Attacks on AHRQ and patient-centered research are misguided and counterproductive," commented ASN Research Advocacy Committee Chair Frank "Chip" Brosius, MD. "Both will yield big savings to Medicare in the long run by improving the delivery of healthcare services and treatments. ASN urges Congress to increase the budget caps and bolster research investments, which is essential for maintaining America's position as the world leader in medical innovation."

In July, the House passed the 21st Century Cures Act, which would also provide NIH additional funding totaling $8.75 billion over 5 years and not be subject to the budget caps. A top ASN legislative priority, the society helped the House Energy and Commerce Committee develop and pass the bill and is now working with the Senate Health, Education, Labor, and Pensions Committee to develop and pass its own version of the bill in the Senate.

"ASN is grateful and urges congressional support for the 21st Century Cures Act that would provide NIH increased funding for 5 years," noted ASN Secretary-Treasurer and Public Policy Board Chair John R. Sedor, MD, FASN. "At the same time, we need to increase the budget caps and provide NIH steady and sustained increases year after year. That is absolutely essential for attracting the best and brightest minds to science and curing our biggest healthcare challenges, including kidney disease."

Save AHRQ and Patient-Centered Research

Tell Congress to save AHRQ and patient-centered research. Take 10 seconds to send your members of Congress a pre-composed email online at https://www.asn-online.org/policy/lac.aspx.

Telehealth in the United States: New Opportunities?

By Mark Lukaszewski

It's clear that patient–provider communications in the United States have not kept up with the rapid evolution in technology. Young kids are communicating with tablets and other devices that put current telehealth iterations to shame. But if we already have the technology, what is the holdup?

Current telehealth policy

One roadblock is that current rules governing telehealth in the United States state that it can only be administered in rural counties and health shortage areas in metropolitan fringes with the patient at a health facility (known as "originating sites"). Also, telehealth services may only be administered by a select group of practitioners and for a select number of medical procedures or services. Store-and-forward technologies (analogous to sending a picture via text message) are only permissible for demonstration projects in Alaska and Hawaii. Remote patient monitoring, a technology that enables patient monitoring of chronic conditions outside of conventional clinical settings, is not a covered telehealth service.

Why try to change it now?

According to the Centers for Medicare & Medicaid Services (CMS), more than 51 percent of patients with kidney disease have five or more comorbid conditions. Effective management of these comorbidities is especially important for patients with earlier stages of kidney disease, during which proper care from a nephrologist may slow progression toward renal failure, as well as prevent the advancement of costly comorbidities caused or worsened by the disease.

Besides improving patient outcomes, facilitating patient access to subspecialists through telehealth may contribute to long-term cost savings—particularly to the Medicare ESRD Program. Currently, approximately 25 percent of all Medicare dollars are spent on care for patients with kidney disease. When CMS reported on the top five most costly triads of chronic illness in 2012, CKD was included in four out of the five with an average cost of approximately $60,000 per capita.

New legislation and what it wants to change

On July 7, 2015, Reps. Mike Thompson (D-CA), Gregg Harper (R-MS), Diane Black (R-TN), and Peter Welch (D-VT) introduced the Medicare Telehealth Parity Act of 2015. This new legislation would allow a patient's residence to serve as an originating site for home dialysis services, and permit them to conduct some monthly clinical assessments via telehealth. As of now, patients who dialyze at home have to travel to a hospital or facility-qualifying site to interface with an approved practitioner.

Providing reimbursement to physicians for caring for patients on dialysis via this telehealth legislation may enable more patients to consider home dialysis as an option, creating greater efficiency for both patients and physicians. Home dialysis—in the form of peritoneal dialysis or home hemodialysis—is an important treatment option that, for some patients, may offer significant clinical and quality of life advantages. Kidney transplant recipients and living kidney donors would also be well served with access to expanded telehealth options. Kidney donor follow-up consultations are mandated by both Medicare and the United Network for Organ Sharing, and typically comprise a simple well-patient visit for which donors must bear the costs of a day off work and travel. Were patient's homes to be designated as an originating site, many of these consultations could easily be provided via telehealth. Clearly, this legislation has the prospect of helping patients with kidney disease of all stages.

Monitoring the system

Although there is wide consensus that telehealth has the potential to improve patient access, reduce hospitalizations, and reduce costs, these hypotheses remain unproven and therefore must be closely evaluated to ensure that the program achieves the intended goals and to ensure that patient safety and quality care remain the number one priority.

The ASN policy team will continue to monitor the progress of this and other kidney-related legislation in Congress and update the membership. Please stay tuned.

To learn more about ASN policy, please visit https://www.asn-online.org/policy/.

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Geriatric Nephrology

ASN Kidney News gratefully acknowledges the editor of this special section, *Kidney News* Editorial Board member Edgar V. Lerma, MD, FASN, for his contributions to this issue.

Renal Senescence: Mechanisms and Implications

By Anette Melk and Roland Schmitt

One of the major challenges for today's society is the growth of the elderly population. By 2030, the age segment over 65 years will have nearly doubled, and the incidence of multiple age-associated disorders is predicted to increase in parallel. Age-associated changes of the kidney are important not only because normal aging alters renal function, but also because of the high frequency of ESRD in the elderly population (1). Moreover, old kidneys perform poorly when they experience acute kidney injury or after transplantation (2, 3), highlighting one of the hallmarks of renal aging—its markedly reduced regenerative capacity. Accumulation of senescent cells during aging and as a result of acute and chronic diseases, along with a certain genetic predisposition, are proposed to be responsible for insufficient repair potential and functional loss (Figure 1) (4–6).

Cellular senescence is a fundamental biologic program resulting in irreversible growth arrest. Senescent cells are still viable and present in the tissue, but they can no longer replicate and thereby regenerate (7). Cellular senescence can result from progressive telomere shortening or as a response to various pathophysiologic stressors (Figure 2). These stressors are not unique to aging and can also occur in certain disease states. Cellular senescence was initially described in human fibroblasts arresting after 50 to 70 cell divisions with short telomeres (8–10). Short unprotected telomeres lead through stabilization of p53 to cell cycle arrest (telomere-dependent senescence) or apoptosis (11). Protection of telomeres is provided through telomere-binding proteins as well as through telomerase (11, 12). The concept of cellular senescence also includes other forms of permanent, irreversible cell cycle arrest, which are reached by DNA damage, oxidative stress, Ras induction, and epigenetic alterations. The cell cycle regulator and tumor suppressor p16INK4a is associated with this nonreplication-dependent growth arrest by acting upstream of retinoblastoma (telomere-independent senescence) (13, 14). The crucial role of p16INK4a in the development of senescence and chronic renal damage is underlined by the protective effect of ablating the INK4a locus (15).

The phenotype of renal aging consists of a loss in renal mass (mainly cortical mass) (16) and renal function (it is important to note that at least a third of older individuals in the respective studies had normal renal function) (17, 18) and of not very specific histologic changes in all renal compartments (glomeruli, tubulointerstitium, and vasculature) (6). In the unchallenged kidney, these aging changes go almost unnoticed. However, senescence of key cells in the kidney is particularly unfortunate when the tissue receives unusual stresses. Injury evokes dedifferentiation, proliferation, and inflammation. If tubular epithelial cells can heal, injury and inflammation resolve with minimal scarring. If the epithelium has a high burden of senescence, its normal healing is hampered, and the ensuing proinflammatory and profibrotic milieu will result in scarring. Fibrosis that is triggered by senescence-associated secreted factors may thereby compensate for exhausted healing potential, putting fibrosis downstream of the primary senescence process.

Old kidneys show a diminished proliferative response of tubular cells (19, 20), even without any preceding damage confirming an intrinsically reduced proliferative capacity (21). The reduced proliferative potential correlates with markers of cellular senescence, such as the expression of the cyclin-dependent kinase inhibitor p16INK4a, senescence-associated-β-galactosidase, and, in human kidneys, with telomere shortening (20–22). Telomerase-deficient mice with severe telomere loss have an increased susceptibility to renal injury and renal dysfunction (23). Markers of cellular senescence have been found in certain renal diseases, such as glomerulopathies, tubulointerstitial nephritis, and hypertensive nephrosclerosis, and in transplants with chronic allograft dysfunction (24–27). Recently, evidence has indicated a role for cellular senescence in the development and progression of diabetic nephropathy (27). Inasmuch as hyperglycemia has been shown to cause accelerated senescence through SGLT2-mediated excessive uptake of glucose (28), SGLT2 inhibitors might have potential use in antagonizing the senescent phenotype of diabetic nephropathy.

Many problems in clinical nephrology of the elderly seem to involve an interaction between cellular senescence and disease stresses. This may contribute to the normal renal senescence phenotype, the acceleration of this phenotype by hypertension and heart failure, the high frequency of ESRD in the elderly, and the massive nephron dropout after the stresses of cadaveric donation. The appeal of studying mechanisms of cellular senescence in nephrology is the potential for predicting these mechanisms or intervening in them. Identification of those who are at risk of ESRD could be followed by strategies to reduce the stresses. It is possible that bypassing cell senescence mechanisms with drugs or gene therapy could extend the life of old kidneys faced with abnormal stresses such as cadaveric donation or renal disease. This may have to be balanced against the potential to increase renal cancer. The role of cell cycle regulatory proteins and senescence mechanisms in chronic stresses such as glomerular diseases, proteinuria, hypertension, and polycystic disease should be explored, even independently of the problem of aging.

Figure 1. Cellular senescence contributes to age-associated reduced renal regenerative capacity

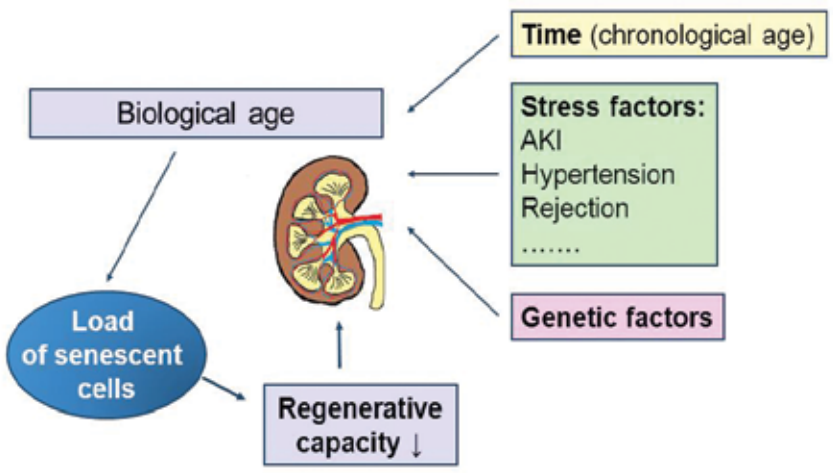
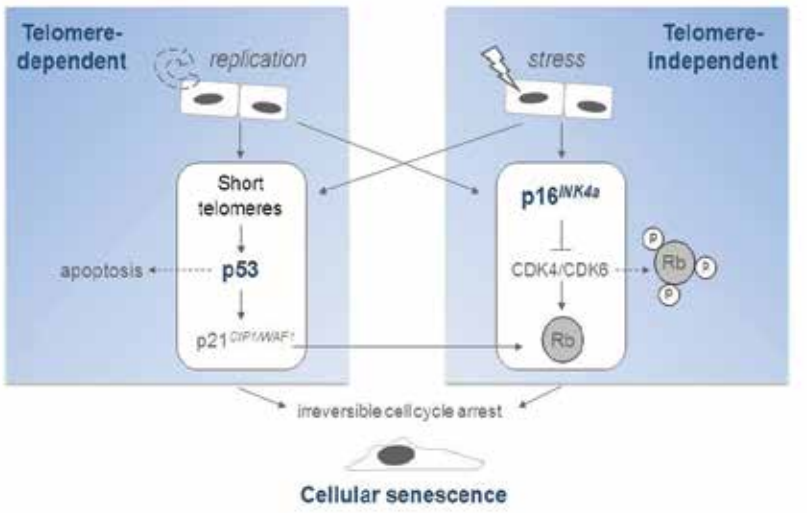


Figure 2. Signaling pathways in cellular senescence



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Caring for Elderly Patients with Kidney Disease: The Geriatrician–Nephrologist Collaboration

By S.A. Balogun and E. Abdel-Rahman

We are aging and living longer. This fact could be attributed to improved technology, medical advances, and the increased number and aging of the baby boomers. It is estimated that the number of elderly will be up to 2 billion by the year 2050 (1). This increase in the number of elderly is mirrored by an increase in medical problems such as acute and chronic kidney disease. This requires coordinated care by multiple specialties, with geriatricians and nephrologists playing a key role in the treatment of these patients.

At least 50 percent of the nephrology patient population are older adults with a wide range of kidney diseases. There has been a steady increase in the percentage of elderly patients with chronic kidney disease (CKD) and ESRD over the years (2). According to the third National Health and Nutrition Examination Survey data, in the United States, almost 40 percent of adults 60 years and older have some degree of chronic kidney disease (3, 4). Some of the structural and physiologic changes in kidney function are the result of normal aging; however, medications such as nonsteroidal anti-inflammatory agents, aspirin, and some herbal preparations are nephrotoxic and are also common culprits contributing to kidney disease in this population. Other risk factors include agents such as contrast dye used in radiologic tests that cause acute kidney injury (AKI), and chronic medical diseases such as diabetes mellitus and hypertension (Table 1).

Structural changes affect all components of the kidney. This results in AKI being more common in older adults. AKI can have several causes: prerenal disorder with decreased volume secondary to poor oral intake with loss of thirst sensation, loss of concentrating ability of the renal tubule, loss of fluid through the gastrointestinal tract and kidney, intrinsic renal processes with ischemic and septic acute tubular necrosis, drug-induced and infection-induced allergic interstitial nephritis, and vascular causes such as atheroembolic diseases and vasculitis. Although patients 80 years and older make up 10 percent of hospital admissions, the prevalence of AKI in this population is about 30 percent, with prerenal disorders secondary to dehydration being the most common cause. Recovery of renal function is also much slower in older adults than in younger individuals, resulting in longer recovery times (5).

Another renal-related medical problem in older adults is the increased prevalence of arterial hypertension. Blood pressure continues to increase with increasing age. Data from the Framingham population heart study suggests that in persons aged 55 years who are not hypertensive, the risk of experiencing hypertension by age 80 is 91 percent, and their lifetime risk is 93 percent (6).

Geriatricians are often asked, "Will I need dialysis, doctor?" This common question is usually posed right after patients are informed that their kidney function is abnormal. Often the news is a surprise to the patient and family

Table 1. Common risk factors for chronic kidney disease in elderly patients

Hypertension
Diabetes mellitus
Cardiovascular diseases
Medications
NSAIDS
Aspirin
Antibiotics (vancomycin, gentamycin)
Herbal preparations
Radiologic contrast dyes

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because the patient typically does not have any symptoms related to kidney disease, or attributes common symptoms of advanced kidney disease such as fatigue, anorexia, and nausea to the aging process or to another medical condition. In fact, some patients assume that if they are producing "normal" amounts of urine, the kidney is functioning optimally.

For patients with early to moderate CKD (stage 1–3), most of the clinical management hinges on controlling factors and diseases that adversely affect kidney function, such as blood pressure control in hypertension, effective diabetes managment, and avoiding nephrotoxic medications and agents. More importantly, effective and optimal communication between geriatrician and patient is key. In addition, close monitoring of kidney function and electrolytes is critically important so the trajectory of change in kidney function can be tracked and can help both the clinician and the patient in developing an appropriate plan of care. For instance, the progression of kidney disease may be very slow in some elderly patients, making it unlikely that they will require renal replacement therapy (RRT) in their lifetime. By contrast, kidney disease could progress rapidly, with a need for imminent RRT. Collaboration between geriatricians and nephrologists is prudent in co-managing kidney disease in these patients, particularly with dietary advice, optimizing hydration when needed, managing electrolyte imbalances, and treating anemia, which may result from iron deficiency, kidney disease itself, or both (Table 2). It is crucial to establish this co-management team early in the disease process because it provides an avenue to optimize the patient's care and facilitates long-term care planning. The patient's goals of care should also be explored, so as to guide the team in tailoring the patient's care to those goals. As with all geriatric patients, a comprehensive geriatric assessment, including cognitive, functional, and psychosocial assessment, is of utmost importance in identifying potential issues and adequately treating these patients as their disease progresses, while enabling them to function optimally in their environment, whether they live independently or require long-term care.

With advanced CKD (stage 4–5), RRT, particularly dialysis, is foremost in most patients' minds, leading to the question above. With this comes a very complicated and careful consideration of a patient's preferences for care, quality of life, and functional and cognitive status. In patients with cognitive deficits, the clinical team may also have to consider the preferences of family members. RRT (hemodialysis, peritoneal dialysis, and renal transplantation) is no longer a novelty in the elderly and can be the right option for many geriatric patients. Indeed, some elderly patients have comparable or even better health-related quality of life when using the different RRT modalities compared with younger patients using RRT or age-matched control individuals (7–10). In addition, home-based dialysis options for suitable patients further promote a good quality of life. In a 2010 study, more than 90 percent of geriatric patients using home-based hemodialysis and peritoneal dialysis were highly satisfied with health services and felt that they had chosen the right mode of treatment (11). This option, however, would obviously be feasible only for the highly motivated elderly patient with optimal physical and cognitive function. Renal transplantation in geriatric patients is also typically considered in the "youngest old," those between 65 and 75 years who are otherwise in good health, with intact physical and cognitive functions.

Overall, the choice of treatment hinges on a thorough and comprehensive discussion among the patient, the family member(s), and the geriatrician-nephrologist co-management team, with careful consideration of the patient's condition and goals of care. It is also important to include conservative palliative management focused on comfort and symptom control as one of the options for care. Often this option is overlooked or omitted, and patients can feel compelled to choose a more aggressive intervention because they perceive there are no other choices. Visser et al. (12) found that some elderly patients chose hemodialysis simply because they felt there were no better alternatives and viewed it as the only way to stay alive. Furthermore, family members can greatly influence the decisions and perceptions of their elderly loved ones, so physicians need to carefully explore the preferences of the patients themselves whenever possible (13). Careful consideration of medical conditions that can influence patients' decisions, such as depression or other psychopathologic conditions like delirium, dementia, and primary psychiatric disorders, is also warranted, and attempts should be made to optimize treatment of these conditions when possible before discussions about goals and preferences for care are undertaken.

Elderly CKD patients with significant cognitive deficits, functional deficits, or both can present a very difficult and ethical dilemma for geriatricians and nephrologists, especially when these patients are deemed not to have decision-making capacity and the clinicians have to rely on decisions made by others such as family members, next of kin, or durable medical power of attorney. This can create several problems, in particular if the decisions made are incongruent with the opinions held by the medical team. Often, rational resolution can be achieved only through very patient and careful dialogue with all parties concerned. Also, engaging these surrogate decision-makers as early as possible in the patient's treatment, and cultivating their trust, is crucial in these situations.

It is also not uncommon for elderly patients receiving dialysis to live in inpatient rehabilitation centers and long-term care institutions, such as assisted living facilities and nursing homes. Up to 0.6 percent of ESRD patients using hemodialysis or peritoneal dialysis reside in a long-term care facility (14). Several inpatient rehabilitation centers provide hemodialysis services on site to avoid disrupting patients' physical and occupational therapy regimens, thereby facilitating their discharge home (15). However, in the majority of nursing homes and assisted living facilities, patients with ESRD receive hemodialysis at off-site dialysis centers. Going to these dialysis centers, often several days a week, may adversely affect the patients' quality of life and limit their ability to participate in the facility's activities.

Overall, the treatment of elderly patients with CKD requires careful coordination, a comprehensive approach to care, and thoughtful collaboration between geriatricians and nephrologists to optimize care. An interdisciplinary team approach is best, with the primary care physician or geriatrician taking the lead in the earlier stages of kidney disease, followed by careful and close interaction between the nephrologist and the geriatrician as the disease progresses, especially in the more complex phases. Whereas nephrologists address acute medical renal issues, long-term preventive care, and management of RRT, geriatricians often address issues with long-term care planning, and assess the socioeconomic and psychological needs of their patients and family members. Furthermore, geriatricians are involved in the preparation of these patients for ESRD care, in exploring the options for RRT, and in addressing end-of-life concerns.

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Table 2 . Clinical co-management of chronic kidney disease in elderly patients

Stage 1–3 (mild to moderate)	Monitoring of kidney function and electrolytes Avoidance of nephrotoxic agents and medications Treatment of risk factors BP control: hypertension Glucose control: diabetes mellitus Management of anemia Iron supplementation Erythropoiesis-stimulating agents Dietary modification Ensuring adequate hydration
Stage 4–5 (severe)	Counseling on goals and plan of care Renal replacement therapy Hemodialysis Peritoneal dialysis Renal transplantation Conservative palliative measures

General Principles of GFR Interpretation in the Elderly

By Naya Huang and Lesley A. Inker

In the United States, chronic kidney disease (CKD)—defined by reduced GFR <60 mL/min per 1.73 m^2, or presence of kidney damage—is very common in the elderly population. The prevalence of CKD is estimated to be 46.8 percent in those older than 70 years (1). However, the significance of reduced GFR in the elderly has been debated, and some suggest that reduced GFR is secondary to (expected) age-related changes in kidney function and is not evidence of true kidney disease. Regardless of the label, elderly patients with reduced levels of GFR are at higher risk for adverse outcomes and complications, and they require modification of drug dosages. Issues related to the accuracy and interpretation of GFR estimates in the kidney are discussed here.

Accuracy of eGFR in estimating mGFR in elderly

Measured GFR is considered the gold standard for evaluation of kidney function; however, it is difficult to perform in routine practice, and estimated GFR (eGFR) is more commonly used. The estimating equations are developed from serum levels of endogenous filtration markers, such as creatinine or cystatin C, in combination with other variables that act as surrogates for unmeasured non-GFR determinants of the filtration markers. The most commonly used eGFR creatinine equations are the Modification of Diet in Renal Disease (MDRD) study equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (1, 2). The MDRD study equation is widely used, but it underestimates GFR at higher levels, thereby overestimating the prevalence of CKD. The CKD-EPI creatinine equation improves on these limitations for adults of all ages, and the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines on the evaluation and management of CKD recommends reporting eGFR from creatinine (3–5).

Creatinine-based eGFR is not always sufficiently accurate for all clinical decision making. For example, it and other filtration markers should not be used in the non–steady state. More importantly, the levels of filtration markers are determined by factors other than GFR. For creatinine, its main non-GFR determinants are muscle mass and protein intake, both of which may be abnormal in the elderly and vary within an individual with changes in health status. For example, in a previously healthy 80-year-old man, a decline in GFR may be masked by weight loss and decreased oral intake. KDIGO recommends the use of a confirmatory test with measured GFR using an exogenous marker, a measured creatinine clearance, or eGFR based on cystatin C in such patients for whom accurate levels of GFR would change management (3–5).

Recent studies have shown that equations based on the combination of creatinine and cystatin C provide more accuracy and precision in GFR estimation than either alone (6–8), and this has been demonstrated in at least two elderly populations (mean age 80 years) (9, 10). One of these studies compared the CKD-EPI equations with other equations also developed using standardized assays for creatinine and cystatin C and showed that the CKD-EPI creatinine, cystatin C, and combined creatinine-cystatin C equations were better than or equivalent to other equations, supporting the KDIGO recommendation to use CKD-EPI equations in the elderly population (9).

Use of GFR estimates in the elderly population

Estimates of GFR are commonly used in practice to detect CKD, evaluate the progression of kidney disease, predict a patient's prognosis, and determine the level of kidney function for drug dosing.

Detection of CKD

The use of more accurate equations leads to more accurate detection and staging of CKD. A large meta-analysis of diverse populations from the Chronic Kidney Disease-Prognosis Consortium (CKD-PC) found that the CKD-EPI creatinine equation more accurately classified individuals into the correct GFR stages than did the MDRD study equation in the general population and in the subgroup with ages ≥65 years (11). Similarly, another meta-analysis of similar cohorts showed that the CKD-EPI creatinine–cystatin C and cystatin C equations reclassified patients with CKD more accurately than did the CKD-EPI creatinine equation in the general population and in the subgroup with ages ≥65 years (12).

Assessment of progression

Change in GFR is the primary way in which progression of kidney disease is evaluated. Despite concerns that changes in GFR may not be sufficiently accurate in the elderly, given possible changes in non-GFR determinants, two large meta-analyses showed that declines in eGFR had strong and consistent associations with subsequent kidney failure and mortality, and these associations were consistent across different ages and with other clinical characteristics (13, 14).

Prediction of prognosis

Lower eGFR levels are associated with risk for adverse events such as cardiovascular disease (CVD), mortality, and ESRD. Data from CKD-PC showed that risk for all outcomes increased at levels below 75 mL/min/1.73 m^2 (15). In a subsequent publication, CKD-PC showed a significant positive interaction between age and GFR for all-cause mortality and CVD mortality, suggesting that lower eGFR had stronger adverse effects at younger ages and weaker effects at older ages (16). Nevertheless, GFR <60 mL/min/1.73 m^2 remains a significant risk factor for mortality and ESRD in older age. Of note, the absolute risk for mortality and CVD mortality with low eGFR was much higher at older age than in younger age categories, and in the elderly population consideration of both absolute and relative risks is critical to understanding risk factors.

Risk for other comorbid conditions

Several studies have demonstrated that lower GFR in old adults is associated with risk for bloodstream infection (17), global cognitive performance (18, 19), and frailty and diminished physical function in the elderly (20–22). These are strongly related to patient safety because they increase the risk of falls, disability, and worsening comorbidities and are important determinants of quality of life and longevity.

Dose adjustment of medication

Older adults are at a higher risk for the development of advanced diseases and comorbidities and, as such, frequently require multiple medications. KDIGO recommends that prescribers use the most accurate method for GFR estimation when drug dosing. The Cockcroft and Gault equation is inaccurate in the era of standardized creatinine assays and is no longer recommended for use (23, 24). Many still use that equation with the misconception that the use of weight overcomes the limitation of creatinine generation, but it does not; in fact, the sharp decline in eGFR with age (i.e., the "140-age" term) that occurs with the Cockcroft and Gault equation leads to a large underestimation of GFR in the very old.

Conclusions

The GFR is fundamental to understanding the nature and severity of kidney disease. There is now solid evidence that eGFR is accurate in the elderly and is appropriate to use to detect and stage CKD, to determine the prognosis and complications of CKD, and to determine the dosing of medications. Creatinine-based estimates are the first-line test and should be confirmed by clearance measurements of cystatin-based estimates of mGFR in appropriate clinical circumstances.

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Hypertension Management in the Elderly Population

By Guity Farahmand, Carol Lee, and Kirsten L. Johansen

Hypertension remains a growing problem in our aging population. Recent data from the National Health and Nutrition Examination Survey (NHANES) estimate that almost one-third of the adult population meets the criteria for hypertension (1). Furthermore, the prevalence increases with age; 65 percent of individuals over the age of 60 are hypertensive. Approximately three-quarters of the population with diagnoses of hypertension require some form of pharmacologic therapy, and the percentage is as high as 82 percent among individuals over the age of 60.

The Framingham Heart Study helped to elucidate the expected trajectory of blood pressure in normotensive and hypertensive individuals with aging. Initially, both systolic (SBP) and diastolic blood pressure (DBP) increase linearly with age. However, SBP and DBP diverge around the fifth to sixth decade, when DBP begins to decline whereas SBP continues to increase (2). Subsequent studies have shown the predominance of isolated systolic hypertension in individuals over the age of 50, have described it as a major predictor of cardiovascular events, and have suggested its importance as a modifiable target (3, 4).

Effects of treatment of hypertension on mortality and on cardiovascular and stroke outcomes

In 2000, a meta-analysis (5) of eight key randomized controlled trials (RCTs), including the Systolic Hypertension in the Elderly Program (SHEP) (6) and the Systolic Hypertension in Europe (Syst-Eur) trial (7), examined total mortality and cardiovascular outcomes in relation to SBP and also evaluated the benefit of antihypertensive therapy on these outcomes. The authors defined systolic hypertension as a value of 160 mm Hg or greater with a DBP of less than 95 mm Hg, excluding some trial participants with diastolic hypertension. In a pooled analysis, higher SBP was associated with higher total mortality (hazard ratio [HR] 1.26; 95 percent confidence interval [CI] 1.13–1.40; per 10 mm Hg) and stroke risk (HR 1.22; 95 percent CI 1.04–1.40; per 10 mm Hg). By contrast, higher DBP was associated with a lower risk of all-cause mortality.

With regard to treatment, the target SBP varied by trial but was generally below 150 mm Hg (8). The results showed decreased total and cardiovascular mortality and reduced nonfatal cardiovascular events, particularly stroke, among the treated patients. A more recent Cochrane Database review included 15 trials with 24,055 patients, with the notable addition of the Hypertension in the Very Elderly Trials (HYVET), and came to a similar conclusion. They estimated a modest reduction in total mortality (relative risk 0.90, 95 percent CI 0.84 – 0.97) and reduction in cardiovascular mortality and morbidity (relative risk 0.72, 95 percent CI 0.68 – 0.77) with treatment of hypertension (9). However, it should be noted that achieved SBP was not less than 140 mm Hg in any of these trials and was often greater than 150 mm Hg. Nevertheless, the SHEP and HYVET trials, which did attain mean SBPs between 140 and 150 mm Hg, also reported favorable outcomes. The Cochrane review included a subgroup analysis of treatment in very elderly patients (80 years or older), which showed no significant benefit in terms of all-cause mortality, including cardiovascular, coronary heart disease, or cerebrovascular disease mortality.

Although clinical trial results provide solid evidence that controlling SBP below 150 to 160 mm Hg improves mortality in the elderly, the optimal target blood pressure is still unclear. Two relatively recent randomized trials have studied strict blood pressure control (SBP less than 140 mm Hg) versus moderate control (SBP 140 to 160 mm Hg) among older individuals and have shown no difference in outcomes, including cardiovascular and cerebrovascular events (10, 11). In addition, a secondary analysis of the International Verapamil-Trandolapril study (INVEST), which compared the efficacy of a calcium antagonist versus a noncalcium antagonist hypertension treatment strategy (12), examined the relationship between blood pressure and adverse outcomes in elderly patients with coronary artery disease (13). The target blood pressure for both arms of the trial was less than 140/90 mm Hg (and less than 130/85 mm Hg in patients with diabetes or renal impairment). In a secondary analysis, outcomes were examined according to achieved blood pressure after the participants were divided into four age categories ranging from less than 60 years to 80 years or older. At baseline, the older participants had higher SBP and the highest prevalence of myocardial infarction (MI), stroke, heart failure, chronic kidney disease, and other comorbid conditions and risk factors for cardiovascular events and death. During the trial, the very old had the highest incidence of adverse outcomes, including death, nonfatal MI, nonfatal stroke, all stroke, and the primary outcome, which combined death, nonfatal MI, and nonfatal stroke. The hazard ratios for the association of SBP during the trial with the combined outcome were "J-shaped" or "U-shaped" for all age groups, but the "optimal" SBP (i.e., the SBP at which the hazard ratio was at its nadir) was higher among older individuals. Whereas risk was lowest at SBPs of 110 to 120 mm Hg among patients under age 70, the lowest risk was at SBPs of 140 to 145 mm Hg for patients 70 and older.

In consideration of these data, members of the Eighth Joint National Committee (JNC 8) recommended more lenient blood pressure goals for individuals aged 60 years and older than in the previous guidelines, setting a target below 150/90 mm Hg (14). Although this target is in agreement with European guidelines (15), there is an interesting difference in that the European guidelines recommend beginning treatment when SBP is above 160 mm Hg to match the population included in the trials showing benefit. Of note, not all members of the JNC 8 panel agreed with raising the target blood pressure to below 150/90 mm Hg in the over-60 age group. The dissenting panel members recently presented a minority view (16) in which they argued that increasing the target will likely lead to a reduction in the intensity of antihypertensive treatment in this group, reversing the decades-long trend of better blood pressure control. They also point out that because older individuals are at higher risk of cardiovascular events than are younger persons, this recommendation for less aggressive treatment applies to the group at the highest absolute risk of adverse events who stand to benefit the most.

The impact of frailty and comorbidity

These disagreements among experts reflect a lack of definitive RCT evidence to determine the optimum SBP for maximal cardiovascular event-free survival among older individuals. It must also be recognized that the elderly population is heterogeneous and includes individuals who are completely independent and robust in addition to those who are frail or even disabled. Therefore, setting blood pressure targets according to age alone may not be prudent. Some who support higher

blood pressure targets in the elderly have emphasized that clinical trial participants represent a relatively healthy subpopulation. In particular, the HYVET study excluded patients with most major comorbid conditions and individuals requiring nursing care (17). In clinical practice, decisions regarding blood pressure targets are particularly difficult in poor-functioning older adults who do not meet the inclusion criteria of the RCTs, and it is not clear whether the risks and benefits in this population differ.

Several studies have raised concerns that aggressive blood pressure treatment may increase the risk of falls in the elderly. A recent study of Medicare beneficiaries over age 70 with hypertension compared the incidence of serious fall injuries among patients receiving no antihypertensive medication, those receiving moderate-intensity, and those receiving high-intensity antihypertensive treatment (18). Antihypertensive medications were associated with a higher risk of serious fall injuries, particularly among patients with a history of previous fall injuries.

Cognitive function is another important determinant of independent living and quality of life among the elderly that might be affected by hypertension or its treatment (either positively or negatively). Although hypertension has been associated with cognitive decline, data on the treatment of hypertension on cognitive function has been conflicting. Although a substudy of the Syst-Eur trial reported a significantly lower incidence of dementia in the treatment group (19), the SHEP and HYVET trials did not show any significant difference between the treatment arms versus placebo (20, 21). Thus, available RCT evidence does not show clear cognitive benefit or harm with treatment of hypertension in the elderly. It is important to note that the relatively short follow-up of some studies could limit the power to detect differences in cognitive function with treatment.

A recent observational study published in the *Archives of Internal Medicine* assessed whether the risk of hypertension varies according to frailty by dividing elderly NHANES participants 65 years and older into three groups according to gait speed over a 20-foot walk: faster (greater than or equal to 8 m/sec), slower (less than 8 m/sec), and unable to complete the test (22). Among individuals with faster gait speed, higher SBP was associated with higher mortality. However, there was no association between SBP and mortality among slow walkers. Furthermore, among individuals who were unable to complete the walk test, the risk of death was actually lower among those with elevated blood pressures. Similarly, a population-based study of individuals aged 85 from the Netherlands showed that although there was no significant association between SBP and stroke overall, the risk of stroke was higher among those with lower SBP in individuals with impaired cognitive or physical function (23). It has been suggested that in frail older adults, higher blood pressure may be necessary to maintain perfusion of vital organs. It is also possible that lower blood pressure among frail elders could be related to underlying malnutrition, heart failure, or other comorbidities, which themselves carry a poor prognosis.

Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population (PARTAGE), a longitudinal study of 1130 frail individuals aged 80 years or older who were living in nursing homes, addressed the association of blood pressure and antihypertensive medications with mortality (24). At baseline, almost 80 percent of the participants were receiving treatment for hypertension, and 63 percent of men and 53 percent of women had an SBP of less than 140 mm Hg. After 2 years of follow-up, there was an inverse relationship between baseline SBP levels and all-cause mortality, even after adjustment for age, sex, comorbidity, and level of independence. Further analysis revealed an interaction between low SBP and treatment with multiple antihypertensive medications, such that mortality risk was higher among those with low blood pressure who were receiving multiple antihypertensive medications (24). These data raise the possibility that hypertension is overtreated among frail nursing home residents.

Treatment recommendations

The RCT data clearly support starting antihypertensive therapy at SBP above 160 mm Hg and lowering to a target between 140 and 150 mm Hg. Experts disagree on how these data should be extrapolated in clinical practice, with some recommending beginning treatment at a lower SBP (greater than 150 mm Hg) (14) or targeting a lower SBP (less than 140 mm Hg) (25), particularly among relatively healthy individuals aged 60 to 79 years. There has been less emphasis on how to reach these goals. Although some have raised concerns about the safety of sodium restriction and weight loss, an RCT showed benefit of salt restriction among individuals aged 60 to 80 years (26). Weight loss among obese participants also resulted in better blood pressure control and fewer cardiovascular events. The American Heart Association and the European Society of Hypertension have emphasized the importance of total blood pressure reduction over the choice of antihypertensive medication based on the results of several studies and meta-analyses comparing different classes of antihypertensives.

Going beyond guidelines, it seems prudent to individualize the decision to treat hypertension according to functional status, life expectancy, and preferences of care, because for some patients, concern about injurious falls may be paramount, whereas other patients may fear the complications of untreated hypertension (27). When antihypertensive drug treatment is indicated, clinicians should use the lowest dose possible to achieve target blood pressure and should monitor patients for orthostatic hypotension, symptoms of hypotension, or worsening of physical functioning.

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Diabetes Management in the Elderly Patient with Kidney Disease

By Mark E. Molitch

Diabetes mellitus is the most common cause of chronic kidney disease (CKD) and kidney failure (1). More than one quarter of the United States population over age 65 has diabetes (2), and 37 percent of them have an eGFR <60 mL/min/1.73 m^2 (3).

Whether the decreased GFR is due to age-related decline or to diabetic kidney disease (see other articles in this issue), it affects the clearance of insulin and many diabetes medications and raises the risk of hypoglycemia (4). Hypoglycemia is the major barrier to achieving near-normal glycemia, which has been shown to delay the progression of diabetic kidney disease (5, 6). If a low GFR is thought to not be due to diabetic kidney disease, then a more relaxed HbA1c goal may be appropriate to avoid hypoglycemia.

Older patients with diabetes are frail, unstable, prone to falls, and at increased risk of hip fracture (7, 8), augmenting the risk of an adverse outcome from hypoglycemia. They also have an increased risk of depression and cognitive impairment while at the same time being treated with myriad drugs; polypharmacy may put them at risk for medication errors and erratic medication adherence (7, 8). Thus, frail elderly individuals are at increased risk for medication-induced hypoglycemia for a variety of reasons in addition to their falling GFR. Severe hypoglycemia is associated with both short-term and long-term increased risk of major macrovascular events, death of cardiovascular causes, and all-cause mortality (4, 9, 10). Low HbA1c levels and insulin treatment are also associated with increased risks of falls and hip fracture (8).

It is important to assess the risks and benefits of adhering to glycemic goals in a given patient (11). According to the recent guidelines from the American Diabetes Association (12), unlike the goal of 7.0 percent for younger adults, 7.5 percent is a reasonable HbA1c goal for relatively healthy older patients who have few coexisting morbidities, have a reasonable life expectancy, and are at low risk for hypoglycemia. For those at intermediate risk with multiple comorbidities or some cognitive impairment, a goal of <8.0 percent is reasonable. For those with poor health with poor long-term outcomes and more severe cognitive impairment, a goal of <8.5 percent is recommended (12). HbA1c levels higher than 8.5 percent are associated with adverse effects of poor wound healing, catabolism with weight loss, and possible dehydration. The older patient with CKD stage 3 would likely fall at least in the intermediate category, so a goal of 8.0 percent or even higher would be appropriate for most such patients, especially if they are taking insulin. Trial data in such patients are sparse, but one study showed that HbA1c levels >9 percent or <6.5 percent were associated with increased mortality in the presence of CKD stage 3 or worse (13).

Diabetes treatment in older patients with CKD

Insulin

Reduced kidney function results in a prolongation of insulin half-life and a decrease in insulin requirements (14). All insulin preparations can be used in patients with CKD, and there are no specific reductions in dosing for patients. An inpatient study that randomized weight-based basal and bolus insulin in patients with a GFR <45 mL/min to 0.5 units/kg body weight versus 0.25 units/kg showed similar glycemic control but significantly less hypoglycemia in the group with the lower weight-based dose (15). A single dose of long-acting basal insulin can be added when oral agents do not obtain satisfactory control with a relatively low risk of hypoglycemia (16). However, the more complicated the regimen (i.e., adding prandial insulin to basal insulin), the more chances of dosing error and hypoglycemia, especially if there is cognitive impairment. Patients with CKD stage 4–5 often have delayed gastric emptying; giving rapid-acting insulin after the meal may be helpful for matching the insulin peak with the time of the postprandial blood glucose peak. Postprandial rapid-acting insulin with dose adjustment for how much was eaten may help in patients with varying food intakes.

Metformin

Metformin increases insulin sensitivity and decreases hepatic gluconeogenesis; it does not cause hypoglycemia. It reduces HbA1c by 1.0 to 2.0 percent and is the first drug generally used when lifestyle changes do not provide satisfactory control (17). The U.S. Food and Drug Administration recommends that metformin should not be used with serum creatinine ≥1.5 mg/dL in men and ≥1.4 mg/dL in women or with decreased creatinine clearance in people over age 80 to reduce the risk of lactic acidosis, which is actually very rare (17). Recently, it has been recommended that metformin be used without dose reduction with an eGFR >45 mL/min/1.73 m^2, with a reduction to 1000 mg daily if the eGFR is ≥30 to 44 mL/min/1.73 m^2 and stopped with an eGFR <30 mL/min/1.73 m^2 or in situations associated with hypoxia or an acute decline in kidney function such as sepsis/shock, hypotension, and use of radiographic contrast medium or other nephrotoxic agents (17) (Table 1).

Sulfonylureas and meglitinides

Sulfonylureas and meglitinides increase insulin secretion and can cause hypoglycemia. Sulfonylureas and their metabolites are renally cleared, leading to an increased risk of hypoglycemia as GFR declines. Glyburide should be avoided with eGFR <60 mL/min/1.73 m^2 (18) and also in the elderly. Glimepiride should be used with caution if the eGFR is <60 mL/min/1.73 m^2 and should not be used with eGFR <30 mL/min/1.73 m^2 (19). Less than 10 percent of glipizide is cleared renally, but it should still be used with caution with an eGFR <30 mL/min/1.73 m^2 (20, 21).

Nateglinide and repaglinide result in a rapid and short duration of insulin release and should be taken before meals. The active metabolite of nateglinide accumulates in CKD; nateglinide should not be used with an eGFR <60 mL/min/1.73 m^2 (22). Repaglinide appears safe to use in CKD (23).

Thiazolidinediones

Pioglitazone and rosiglitazone increase insulin sensitivity and do not cause hypoglycemia. They are hepatically metabolized and can be used in CKD without dose adjustment. However, fluid retention is a major adverse effect, which may worsen heart failure and makes the use of these agents in CKD limiting. They are associated with increased fracture rates and bone loss in women (24); thus, their use in patients with underlying bone disease (such as renal osteodystrophy or osteoporosis) potentially could be problematic.

Alpha-glucosidase inhibitors

Acarbose and miglitol decrease the breakdown of oligosaccharides in the small intestine, delaying the absorption of glucose after a meal, and do not cause hypoglycemia. Neither drug has been studied over the long term in patients with creatinine >2 mg/dL, so their use should be avoided in these patients.

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin) decrease the breakdown of incretin hormones such as GLP-1 and do not cause hypoglycemia. All but linagliptin have some renal clearance and need dose adjustment in patients with reduced eGFR (25, 26) (Table 1). In general, they are very well tolerated, and there are no special concerns for the elderly.

Sodium-glucose cotransporter 2 inhibitors

Sodium-glucose cotransporter-2 inhibitors reduce glucose reabsorption in the proximal tubule, leading to an increase in glucose excretion, a reduction in A1c of ~0.8 percent, and weight loss; they do not cause hypoglycemia. Because of a small increase in adverse events related to intravascular volume contraction, no more than 100 mg once daily of canagliflozin should be used in patients with an eGFR of 45 to <60 mL/min/1.73 m^2 (27). Canagliflozin and empagliflozin should be stopped if the eGFR is <45 mL/min/1.73 m^2 and dapagliflozin stopped at 60 mL/min/1.73 m^2, primarily because of a decrease in efficacy.

Glucagon-like peptide-1 receptor agonists

Exenatide, liraglutide, dulaglutide, and albiglutide are injectable glucagon-like peptide 1 receptor agonists, leading to increased insulin release, delayed glucagon secretion, delayed gastric emptying, and appetite suppression with weight loss; they do not cause hypoglycemia. Clearance of exenatide decreases with declines in GFR (28). Cases of acute renal failure associated with exenatide use have been reported, and it should not be used if the GFR is <30 mL/min/1.73 m^2 (29). Liraglutide is not metabolized by the kidney, and no dose adjustment is indicated in those with renal impairment, including ESRD, although data in this population are limited (30). No dose changes are needed for dulaglutide or albigutide with worsening renal function. Nausea is a common side effect and potentially could be problematic in older patients with compromised intake.

Strategy for glycemic control

Glycemic control should be optimized individually for the patient, attaining the necessary control to reduce complications but done in a safe, monitored manner. Usually one or two oral agents or a glucagon-like peptide-1 receptor agonist are added to metformin in a stepwise fashion; if control is still not achieved, basal insulin can be added. If prandial insulin is ultimately needed, special care is needed to avoid hypoglycemia.

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Table 1. Dose adjustment for insulin and other medications used to treat diabetes*

Medication Class	CKD Stages 3–5†
Insulin Glargine, detemir, NPH, regular, aspart, lispro, glulisine	No specific dose adjustment; decrease doses depending on patient responses
Sulfonylureas Glipizide Glimepiride Glyburide	 eGFR <30: use with caution eGFR <60: use with caution, <30 avoid use eGFR <60: avoid use
Glinides Repaglinide Nateglinide	 eGFR <30: use with caution eGFR <60: avoid use (can use if dialysis)
Biguanide Metformin	Per FDA: do not use if creatinine ≥1.5 mg/dL in men and ≥1.4 mg/dL in women *Consider (controversial, not FDA approved)*: eGFR 45–59: use caution, follow renal function every 3–6 mo eGFR 30–44: max dose 1000 mg/day, follow renal function every 3–6 mo; do not start as new therapy eGFR <30: avoid use
Thiazolidinediones Pioglitazone, rosiglitazone	No dose adjustment needed
α-glucosidase inhibitors Acarbose, Miglitol	Serum creatinine >2 mg/dL: avoid use
DPP-4 inhibitors Sitagliptin Saxagliptin Alogliptin Linagliptin	 eGFR ≥50: 100 mg daily eGFR 30–49: 50 mg daily eGFR <30: 25 mg daily eGFR >50: 2.5 or 5 mg daily eGFR ≤50: 2.5 mg daily eGFR >60: 25 mg daily eGFR 30–59: 12.5 mg daily eGFR <30: 6.25 mg daily No dose adjustment needed
SGLT2 Inhibitors Canagliflozin Dapagliflozin Empagliflozin	 eGFR 45–60: max dose 100 mg daily eGFR <45: avoid use eGFR <60: avoid use eGFR <45: avoid use
GLP-1 Receptor agonists Exenatide Liraglutide, dulaglutide, albiglutide	 eGFR <30: avoid use No dose adjustment needed
Dopamine receptor agonist Bromocriptine	No dose adjustment known but not studied; use with caution
Bile acid sequestrant Colesevelam	No dose adjustment needed but limited data

***Abbreviations: CKD = chronic kidney disease; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated GFR; FDA = U.S. Food and Drug Administration; GLP = glucagon-like peptide; SGLT2 = Sodium-glucose cotransporter-2.**

†For all eGFR values, the units are mL/min/1.73 m².

Challenges Associated with the Management of Nutritional Needs in Elderly Patients with Chronic Kidney Disease

By Adnan Naseer and Csaba P. Kovesdy

In the United States we are currently experiencing the phenomenon of the "graying of America," whereby the population is growing older and the proportion of those 65 years and older is rapidly increasing. Data from the U.S. Census Bureau predict that the number of individuals 65 years and older will double in the next 20 years. Most of this growth is happening in the "oldest old"—that is, 85 years and older. Among other challenges, the aging of the population brings the increasing burden of chronic disease conditions such as diabetes, hypertension, and heart disease (1), all of which are known risk factors for chronic kidney disease (CKD) (2). In addition, aging is associated with many changes, including those that have an adverse impact on physiologic, metabolic, and functional status. Specific changes in body composition and the function of organ systems alter the requirements for energy, fat, protein, micronutrients, and fluids.

It has been shown that markers of malnutrition—including hypoalbuminemia, hypocholesterolemia, and low body mass index—are associated with poor outcomes such as increased hospital length of stay, complications, readmissions, functional impairment, and mortality (3–5). This leads to higher use of health care resources by the elderly population. Hence, it is extremely important that malnutrition in elderly persons is recognized early and treated appropriately.

Advancing age is characterized by a progressive loss of lean body mass and a relative increase in fat mass (6). There is also redistribution of fat from peripheral to central locations within the body. Most of the loss in lean body mass is due to reduction in muscle mass, a condition called sarcopenia. The muscle content of the body is important because of the central role of muscle mass in physical function and strength, and because of the association of sarcopenia with increased morbidity and mortality (7, 8). A lack of physical activity is crucial to the development of sarcopenia but is not the sole cause of it. Various hormonal, neural, and proinflammatory cytokines seem to play a role as well (9).

Malnutrition is an important problem that is seen in elderly community-dwelling individuals (10) and in those who are institutionalized (11). Many changes associated with aging can promote malnutrition. Poor appetite is a major cause. Energy and protein intake decrease with age (12), and this decrease can lead to nutritional deficiencies. Various hormones and cytokines (13) are thought to be involved in the regulation of appetite, and age-related changes in these can lead to decreased appetite and early satiety. Changes in taste and smell sensations can lead to loss of appetite through a perceived decline in the pleasantness of food (14). Deteriorating oral health and dentition have been shown to significantly affect food intake. The UK National Diet and Nutrition Survey showed that energy and protein intake is lower in edentate individuals.

Many disease states are associated with higher rates of malnutrition in the older populations. Declining cognitive state, depression, and other psychological factors have been associated with weight loss and malnutrition in the elderly. In addition, many medications have adverse effects that can alter the taste sensation and the appetite, thus further exacerbating nutritional deficiencies.

The dietary protein requirements of the elderly are believed to be higher, and for many reasons. The phenomenon of anabolic resistance leads to resistance to the positive effects of dietary protein on the synthesis of protein (15). Conditions associated with chronic inflammation, such as heart failure, CKD, and chronic obstructive pulmonary disease, add to protein needs. Hence, the imbalance due to increased protein needs and decreased protein intake leads to negative nitrogen balance, which in turn is responsible for frailty and sarcopenia in the elderly. These conditions can lead to functional dependence, falls, fractures, and even death.

Frailty and sarcopenia can be prevented to an extent by increasing protein energy intake and by regular exercise (16, 17). Studies have shown that aging muscle does respond to exercise. Progressive resistance training in older adults can lead to improved physical function (18).

The protein needs of older people may be somewhat higher than was originally thought. The recommended dietary allowance (RDA) for protein in healthy adults of all ages has been set at 0.8 g/kg body weight/day. However, there is evidence to support an increase in the RDA for protein to 1.0 to 1.2 g/kg body weight/day for adults older than 65 years (19, 20). Under conditions of stress or injury, protein requirements are even higher and are estimated at 1.5 g/kg body weight/day. These needs have to be balanced with requirements in certain disease states such as renal or hepatic insufficiency, which may require protein restriction to prevent worsening of these conditions and the development of further complications. This is particularly important in patients with CKD, in whom an uncontrolled high-protein diet may have harmful effects on the progression of kidney disease and on various other metabolic abnormalities. Before a high-protein diet is recommended to an elderly person with CKD, it is thus important to assess the risk of progression of kidney disease versus the risk for development of malnutrition. Mild kidney disease in an elderly person is unlikely to progress to ESRD; hence, a normal-protein or high-protein diet is recommended. In elderly patients with moderate CKD (i.e., estimated GFR of 30–60 mL/min/1.73 m^2) the risk versus benefit needs to be assessed before any dietary protein recommendations can be made. On the other hand, in elderly patients with severe CKD (estimated GFR <30 mL/min/1.73 m^2) protein intake of 0.6 to 0.8 g/kg body weight/day is recommended unless there is a clear indication of a need for higher intake (21).

In summary, elderly individuals experience changes in body composition and therefore protein and energy demands change, making malnutrition a greater risk. Although adequate protein intake is important, the presence of liver and kidney disease needs to be carefully considered before any dietary protein recommendations are made.

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Drug Dosing in the Elderly with Chronic Kidney Disease

By Rachel W. Flurie and Gary R. Matzke

Chronic kidney disease (CKD) is a prevalent disease in the United States that disproportionately affects the elderly. The national prevalence is approximately 15 percent and reaches nearly 50 percent in adults aged 70 years and older (1). CKD stages 1 and 2 are characterized by a GFR >60 mL/min/1.73 m^2, and dose adjustments are usually indicated only for drugs that have a narrow therapeutic index, such as aminoglycosides and vancomycin. CKD stages 3, 4, and 5 are characterized by progressively lower GFR—30 to 59, 15 to 29, and <15 mL/min/1.73m^2, respectively—and drug dose adjustment becomes particularly important for these patients.

Advancing age makes drug dosing challenging because elderly patients often experience adverse drug effects at lower exposure levels than do younger patients; have multiple comorbidities, such as obesity and diabetes, that may independently affect drug pharmacokinetics; and experience polypharmacy with its heightened risk of undesirable outcomes (2, 3). Despite the availability of drug dosage recommendations in the product information approved by the U.S. Food and Drug Administration (FDA), as many as 19 to 69 percent of drugs prescribed for elderly CKD patients exceed the recommended dose (4). Thus, it is crucial that clinicians 1) identify the renal function of the elderly CKD patient, 2) recognize the need for drug dose adjustment (i.e., most commonly due to alterations in drug pharmacokinetics), and then 3) prescribe the appropriate dosage regimen based on the FDA-approved product information or widely available resources (5–7).

Determining a patient's kidney function

The first step is to assess or estimate the patient's kidney function. Traditionally, the estimation of creatinine clearance (eCrCl) has been the primary index of kidney function in clinical practice for drug dosing. During the past 10–15 years, many health systems and outpatient clinical laboratories have begun to report estimated GFR (eGFR) to enhance the identification and staging of patients with CKD, and some have proposed that eGFR replace eCrCl for drug dosing (8, 9). Multiple equations based on creatinine, and more recently, creatinine and cystatin C, have been developed to calculate eGFR. Currently, most clinical laboratories in the United States use the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation because it provides a more accurate eGFR throughout the full range of kidney function. The reporting of eGFR by clinical laboratories has enhanced the identification of adult patients with CKD, but it has not significantly contributed to an improvement in drug dosage adjustment outcomes as one might have anticipated (4).

The pharmacokinetic data suggest that eGFR generally correlates with eCrCl and can be used for staging of CKD and for drug dose adjustment for patients when the eGFR, expressed as mL/min/1.73 m^2, is re-expressed in mL/min before drug references are consulted (9). This requires determination of the patient's weight and height, two clinical values that are not often accurately recorded (3). However, the CKD-EPI equation, which is preferred for CKD staging, overestimates kidney function in elderly patients relative to eCrCl, and the resultant discordance in dosing recommendations may be problematic (10, 11). Thus, if eGFR is used as reported, larger doses may be recommended, possibly leading to higher costs and increased risk of adverse drug effects. For drugs with a broad therapeutic index (e.g., antihypertensives or antidiabetics) this may not be clinically significant, and using eGFR may be acceptable. For drugs with a narrow therapeutic index, eCrCl is preferred. In cases where drug effectiveness is critical or the risk of toxicity is high and associated with serum concentrations (e.g., antibiotics, immunosuppressants, or antiepileptics), monitoring serum drug concentrations is recommended.

Influence of age and CKD on drug pharmacokinetics

The absorption, distribution, metabolism, and excretion of many drugs are altered by impaired kidney function and aging and, when significant, are the foundation for the generation of drug dose adjustment strategies (Table 1) (12–15).

Absorption

No consistent significant alterations in gut absorption have been reported in elderly CKD patients. The bioavailability of some drugs (e.g., levodopa, metoprolol, dextropropxyphene, felodipine, sertraline, and dihydrocodeine) is increased because of decreased presystemic gut and liver metabolism.

Distribution

The volume of distribution of many hydrophilic drugs (e.g., aminoglycosides, penicillins, and cephalosporins) is increased as a consequence of reduced muscle mass, increased total body water, or reduced protein binding, which are often seen in elderly CKD patients. Decreased serum albumin is associated with increased unbound drug fraction and volume of distribution for phenytoin, furosemide, and ceftriaxone, among others. One should start with the typical dose and then monitor unbound drug concentrations or pharmacodynamic response to assure optimal patient outcomes.

Metabolism

Drug metabolism may be reduced in elderly CKD patients as the result of reductions in liver blood flow and the intrinsic activity of cytochrome oxidative enzymes. Emerging clinical evidence suggests that accumulation of uremic toxins may be responsible for the activity of cytochrome oxidative enzymes and transporter proteins (13). Prediction of the degree of effect of aging or CKD on the metabolism of a particular drug is problematic because there is no quantitative correlation even among drugs within the same pharmacologic class.

Excretion

For drugs that are predominantly (>30 percent of total clearance) eliminated by the kidneys, progressive reductions in GFR associated with CKD or aging can reduce renal clearance, and the resultant drug accumulation may lead to exaggerated effects or toxicity at normal doses. In addition to physiologic reductions in glomerular filtration, tubular secretion may be impaired and contribute to marked reductions in renal drug clearance. The elderly and those with CKD stages 3 to 5 are also more prone to acute kidney injury from drugs that cause direct damage or alter renal hemodynamics (e.g., aminoglycosides, angiotensin-converting enzyme inhibitors, and nonsteroidal anti-inflammatory drugs) and are slower to recover from an insult. Given that the measurement of GFR or creatinine clearance is challenging and costly, eCrCl should be used to guide therapeutic decisions, and for drugs with a narrow therapeutic index, monitoring serum drug concentrations is recommended.

Optimal prescribing for the elderly CKD patient

Drug prescribing for the elderly CKD patient starts with identification of the patient's kidney function and awareness of the known impact of aging and CKD on drug pharmacokinetics. A systematic approach to these variables, with FDA-approved dosage recommendations (available from multiple sources) for initial therapy, has the highest likelihood of achieving the patient's individual treatment goals (Table 2) (5–7). Drug dosing recommendations for the most frequently prescribed and

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Table 1. Pharmacokinetic changes due to aging and chronic kidney disease

Pharmacokinetic Parameter	Age-Related Changes	Chronic Kidney Disease Changes	Impact on Drug Dosing*
Absorption	Reduced splanchnic blood flow; gastric acid production, gastric emptying rate, and absorptive surface	Decreased intestinal metabolism; decreased P-glycoprotein activity	Minimal for most drugs
Distribution	Increased body fat; decreased muscle mass; decreased total body water; decreased serum albumin; increased α1-acid glycoprotein	Decreased serum albumin; increased total body water	Moderate for some drugs (e.g., phenytoin, theophylline, digoxin, aminoglycosides)
Metabolism	Reduced hepatic mass; decreased hepatic blood flow; decreased hepatic metabolic activity	Decreased function of cytochrome oxidative 450 enzymes and drug transporter proteins	Moderate for some drugs (e.g., nortriptyline, morphine, warfarin)
Elimination (renal)	Reduced renal mass; decreased renal blood flow; decreased GFR; renal tubular atrophy	Decreased GFR; impaired tubular secretion and reabsorption; increased proteinuria	Major for drugs that are extensively renally eliminated (e.g., cimetidine, sitagliptin, lisinopril)

***Minimal = no dosing impact anticipated; Moderate = some drugs may require monitoring and dose adjustment; Major = accurate dose adjustment and drug monitoring are required.**

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Drug Dosing

Continued from page 17

highest-cost drugs for Medicare beneficiaries and for other commonly prescribed medications in the elderly are listed in Table 3 (5, 6, 16).

The key to optimize elderly CKD patient outcomes is for clinicians to understand the rationale for drug dose adjustment and to use the appropriate resources to individualize therapy. The concomitant presence of obesity or malnutrition or of other chronic diseases that affect drug pharmacokinetics and response such as heart failure and liver disease further complicates therapy decisions and patient outcomes.

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Table 2. Stepwise approach to drug dosing in the elderly patient with chronic kidney disease*

1. Obtain pertinent patient medical history—comorbidities, comprehensive medication history, physical examination, laboratory data
2. Assess renal function—eGFR for drugs with broad therapeutic index and eCrCl for drugs with narrow therapeutic index
3. Review current medications—consider the risk of adverse effects, need for dose adjustment, and contraindications (e.g., www.uptodate.com or www.epocrates.com)
4. Individualize the medication regimen—consider goals of treatment, need for a loading dose, maintenance dosing
5. Monitor drug efficacy/toxicity—patient signs and symptoms, therapeutic drug monitoring when applicable
6. Revisit and revise—adjust medication regimen based on pharmacotherapeutic response and changes in renal function

***Abbreviations: eCrCl = estimation of creatinine clearance; eGFR = estimated GFR.**

Table 3. Dosing recommendations for selected drugs in elderly patients with chronic kidney disease*

Drug	Dose Adjustment Recommendations†		
	GFR = 30–50 mL/min	GFR = 10–30 mL/min	GFR <10 mL/min
Atenolol	25–50 mg q24h		25 mg q24h
Cimetidine	reduce dose 50%		reduce dose 75%
Ciprofloxacin	reduce dose 50%	reduce dose 50%; administer q18h	reduce dose 50%; administer q18–24h
Duloxetine‡	usual dose	avoid use	
Famotidine	reduce dose 50% OR dose q36–48h		
Gabapentin	300 mg q12–24h		300 mg q48h
Glipizide	reduce dose 50%		
Lenalidomide‡	reduce dose 50%	reduce dose 75% OR reduce dose 25% and administer q48h	
Levofloxacin	reduce dose 50% OR administer q24–48h		reduce dose 50%; administer q48h
Lisinopril†	reduce dose 25–50%		reduce dose 50–75%
Metformin‡	reduce dose 75%		avoid use
Olmesartan	usual dose	use with caution	reduce dose 50%
Pregabalin	reduce dose 50%	reduce dose 75%	reduce dose 75–90%
Rosuvastatin‡	usual dose	5–10 mg q24h	
Saxagliptin	reduce dose 50%		
Simvastatin‡	usual dose	5 mg q24h	
Sitagliptin‡	reduce dose 50%	reduce dose 75%	
Solifenacin	usual dose	reduce dose 50%	
Sulfamethoxazole-trimethoprim	dose q12–18h		dose q24h
Tolterodine	usual dose	reduce dose 50%	

***Abbreviations: q12h = every 12 hours; q18h = every 18 hours; q24h = every 24 hours; q36h = every 36 hours; q48h every = 48 hours.**
†May use eGFR or eCrCl to approximate GFR.
‡Included in the top 10 drugs by 2013 Medicare claims or costs.

Geriatric Issues in the Elderly Dialysis Population

By Jennifer S. Scherer and Markus Bitzer

The United States ESRD population is aging. Patients over the age of 65 have the highest adjusted prevalence of ESRD (Figure 1) (1). As a result of these demographics, nephrology providers are now faced with the task of recognizing and treating not only the burdens of ESRD but also morbidities associated with geriatric syndromes (Table 1). Prognosis for the elderly encompasses survival as well as effects on quality of life (QOL), cognition, functional status, and time lost from being with family. Treatment choice and follow-up care should address these issues while considering the individual's preferences, physiological state, and social support. Given that elderly dialysis patients will likely die while receiving dialysis, it would be beneficial to discuss end-of-life choices when dialysis is started.

Unique issues in older dialysis patients

Dialysis therapy does not seem to preserve functional status or independent living for many older patients, with the most vulnerable time being when it is first initiated (2, 3). Older patients receiving hemodialysis (HD) show a high prevalence of functional disability and dependence (3). The consequences of normal aging combined with dialysis-associated adverse events, such as posttreatment hypotension, place an already functionally challenged population at risk for falls. In patients over the age of 65, an accidental fall increases the risk of death in both HD (hazard ratio [HR] 1.78, 95% confidence interval [CI] 1.07–2.98) and peritoneal dialysis (PD) populations (HR 1.62, 95% CI 1.29–2.02) (4, 5). The American Geriatrics Society recommends that all older people be screened for falls (6). They endorse a multifactorial fall risk assessment if the screening results are positive. Empowering members of multidisciplinary dialysis teams to perform fall screenings and functional assessments is a simple way to identify patients appropriate for a more detailed geriatric assessment, and possibly improve QOL.

In addition to functional decline, many ESRD patients are also at risk for cognitive and executive function impairment (7). This deficiency can have an impact on complex thinking, compliance, QOL, and decision-making (7). In a recent study of HD patients, decreased executive function was associated with increased mortality, even with adjustment for comorbidities (7). PD has been shown to have a lower risk of dementia than HD (HR 0.74, 95% CI 0.64–0.86), although both groups have a higher incidence than age-matched control individuals not receiving dialysis (8). Identification of elderly patients with impaired cognition recognizes those who need assistance with decision-making, the responsibilities of dialysis, and caregivers who are at risk for burnout.

QOL, decision-making, and the individualized geriatric experience

As a result of multi-morbidity, the ESRD experience for the elderly is variable. Unfortunately, current guidelines are disease oriented and with a "one size fits all" approach that pays little attention to QOL. Nephrology providers are challenged to integrate the individual patient's experience into appropriate clinical management.

There is no right answer for an elderly patient. A highly comorbid individual may want a trial of dialysis to enable living to a family milestone. An institutionalized patient requiring rehabilitation may be given more free time with PD. If a patient is interested only in survival, recent work from Korea showed an advantage with HD versus PD for the elderly, particularly those with diabetes mellitus or a longer dialysis vintage (9). However, this contrasts with older data that showed no difference in survival and, perhaps more importantly, no difference in QOL (10). For those with a high comorbidity burden, including ischemic heart disease, observational data have shown that dialysis does not confer a survival advantage when compared with conservative management with the incorporation of palliative care (11). Additionally, a recent single-center study demonstrated that integrating palliative care with conservative management led to improved or stable symptom control and QOL metrics at 12 months in a majority of patients (11). The individualized nature of this decision emphasizes the importance of communication; yet, older ESRD patients report feeling unprepared for the HD experience (12). Unfortunately, the burdens of dialysis and the option of conservative management are often excluded from conversations about treatment decisions (13).

Goal-directed therapy: time-limited trials

Given the risk of further suffering from geriatric syndromes in patients receiving dialysis, it is important to check in with patients regularly to assess their dialysis experience. A time-limited trial begins with the identification of patient-specific goals, often relevant to QOL and geriatric syndromes, with planned re-evaluations to assess the patient's perceptions of the benefits and burdens of dialysis (14). This continuous dialogue also allows for a fluid transition into advance care planning. Advance care planning with dialysis patients can promote the use of hospice, a benefit often underused in this population (15). In the general population advance care planning is associated with fewer intensive procedures at the end of life, death at the location of choice, increased patient satisfaction, and increased use of hospice (16).

In summary, the current demographics of ESRD necessitate a cultural shift in care to an individualized approach that incorporates basic principles of geriatric medicine and palliative care. How to best achieve this goal with use of our own dialysis centers' interdisciplinary teams is currently not clear. Although more research and education are needed, it appears obvious that the implementation of geriatric and palliative care principles will enhance current practice and allow the patients' experience to be the largest factor.

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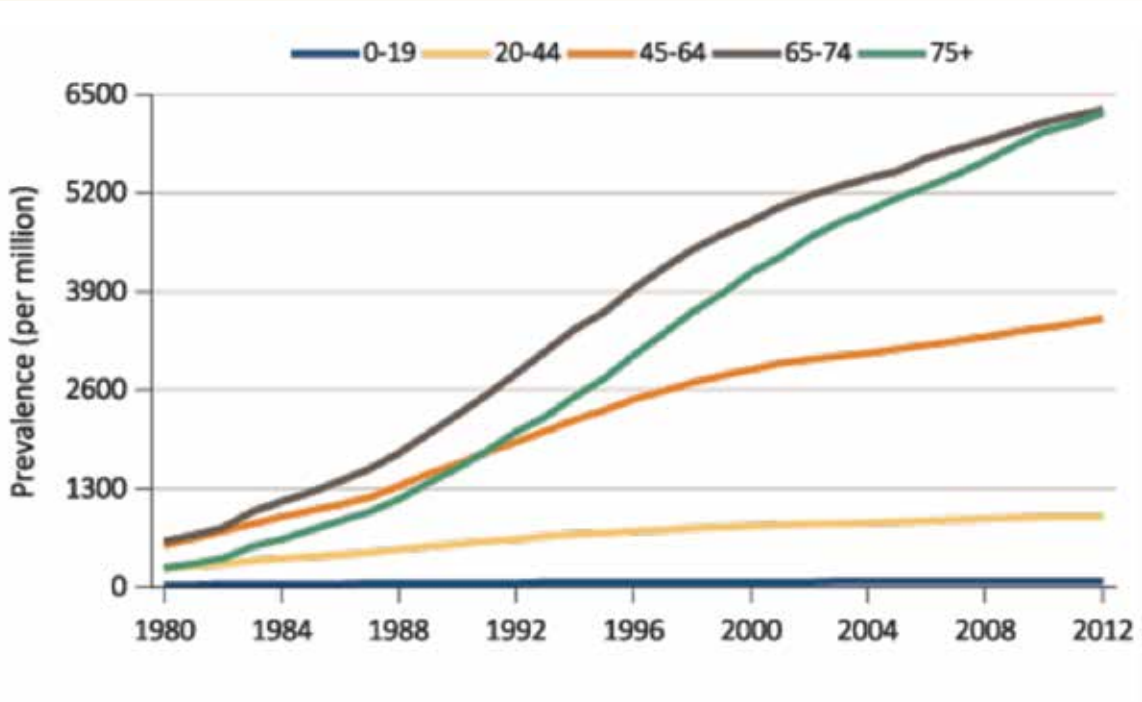
Table 1. Common geriatric syndromes

Falls
Cognitive dysfunction
Gait problems
Vision/hearing loss
Malnutrition

Figure 1. Adjusted prevalence of ESRD, per million, by age group, in the United States population, 1980 to 2012



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Geriatric Issues

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Kidney Transplantation in the Elderly

By Aneesha Shetty and John J. Friedewald

Epidemiology

Although there has been an overall slowing of incident cases of ESRD in the United States during the past several years, the elderly population continues to have the highest incident rates of ESRD (1) (Figures 1 and 2). This has significant implications for transplant centers, which are seeing a continual increase in the age of potential transplant recipients coming for evaluation. The continuing accumulation of data on outcomes in these patients should better inform the risks and benefits of transplantation as therapy for ESRD compared with dialysis. Also, as regulations tighten with regard to observed versus expected outcomes for transplant recipients, elderly ESRD patients face the potential for a decrease in access to transplantation—given their lower levels of graft and patient survival in comparison with younger candidates—despite in many cases still deriving an advantage in survival, quality of life, or both compared with dialysis.

Figure 1. Rates of ESRD in the US

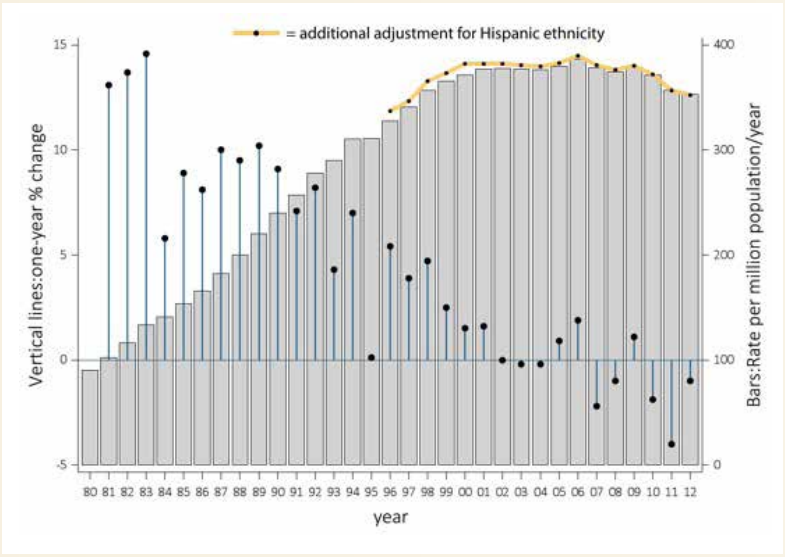
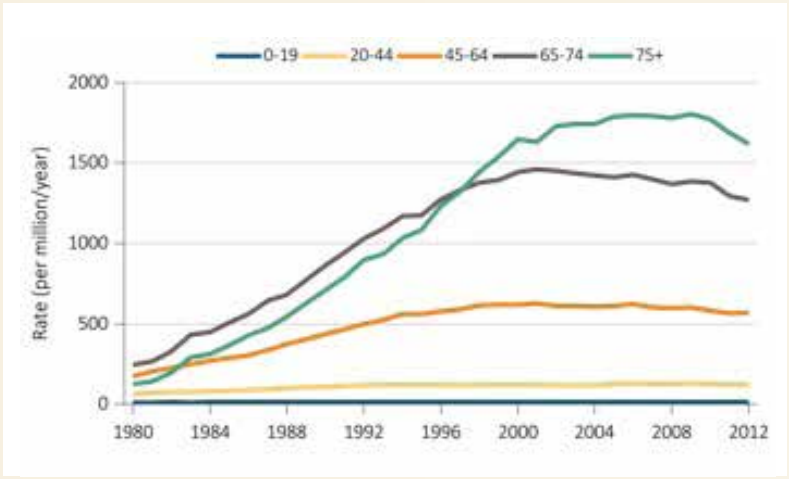


Figure 2. US rates of ESRD by age group



Candidacy

Kidney transplantation remains the treatment of choice for ESRD in elderly patients, providing a survival advantage and better quality of life when compared with dialysis (2). This benefit is especially seen with early transplantation, often facilitated by shorter wait times with the use of kidneys from donors with Kidney Donor Profile Index (KDPI) higher than 85 or living donor transplants. However, the benefit of transplantation in the elderly is contingent on selection of the appropriate candidate. Advanced age is often considered a relative contraindication for transplantation, but there is much variability in the actual age limit for transplantation among transplant centers in the United States. Moreover, chronological age alone seems to be a less important predictor of poor outcomes after transplantation when compared with factors like comorbidity burden, disability, and frailty. Cardiovascular disease, risk of infection, and malignancy are associated with poor outcomes in elderly transplantation patients and should be carefully evaluated during the pretransplantation screening process. Evaluation of activities of daily living and tests like "Timed Up and Go" are often used as a measure of disability. Assessment of cognitive impairment is crucial in elderly transplant recipients, given the higher risk for dementia resulting from vascular disease and metabolic derangement. Elderly patients are also more at risk for depression and are often in need of greater social support compared with their younger counterparts, and hence should undergo a careful psychosocial evaluation.

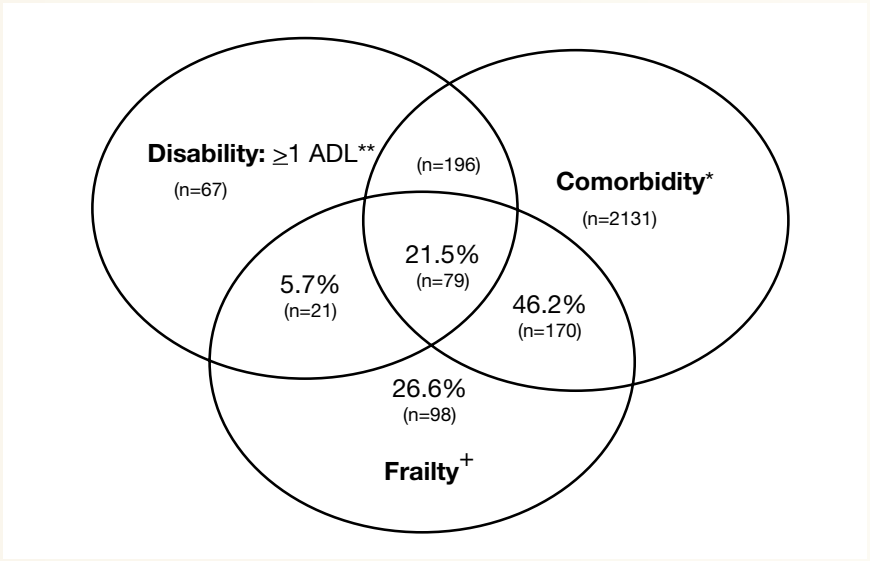
Frailty

Frailty has been recently shown to be an independent predictor of poor outcomes after kidney transplantation, including poor graft function, increased hospitalizations, and perioperative complications (3). The frailty phenotype meets three or more of the following five criteria: weight loss, exhaustion, weakness, slow gait, and decreased physical activity (Table 1) and can be evaluated by the use of different measures. Although frailty, typically characterized by sarcopenia, is often considered a precursor to disability, the relationship between frailty, disability, and comorbidty is complex, as shown by Fried et al. (4) using data from the Cardiovascular Health Study (Figure 3). Evaluation of frailty domains would be an important addition to the pretransplantation screening process in elderly candidates and may allow for better risk stratification and decisions about candidacy.

Table 1. Frailty characteristics

A. Characteristics of Frailty	*B. Cardiovascular Health Study Measure*[+]	
Shrinking: Weight loss (unitentional) Sarcopenia (loss of muscle mass)	Baseline: >10kbs lost unintentionally in prior year	males:<383 Keals/week females: <270 Keals/ week
Weakness	Grip strength: lowest 20% (by gender, body mass index)	*C. Presence of Frailty*
Poor endurance; Exhaustion	"Exhaustion" (self-report)	Positive for frailty phenotype: ≥ 3 criteria present
Slowness	Walking time/15 feet: slowest 20% (by gender, height)	Intermediate or prefrail 1 or 2 criteria present
Low activity	Keals/week: lowest 20%	

Figure 3. Venn diagram displaying extent of overlap of frailty with ADL disability and comorbidity (≥2 diseases).



Total represented: 2762 subjects who had comorbidity and/or disability and/or frailty. *n* of each subgroup indicated in parentheses. +Frail: overall *n*5368 frail subjects (both cohorts). *Comorbidity: overall n 52,675 with 2 or more out of the following 9 diseases: myocardial infarction, angina, congestive heart failure, claudication, arthritis, cancer, diabetes, hypertension, COPD. Of these, 249 were also frail. **Disabled: overall *n*5363 with an ADL disability; of these, 100 were frail.

Allocation

In December 2014, after nearly a decade of deliberation, a new kidney allocation system (KAS) was put into effect by the Organ Procurement and Transplant Network (OPTN). The effect of this new KAS on the elderly was carefully considered by the OPTN Kidney Committee. Elderly patients have received an increasing percentage of deceased donor kidneys over the past 2 decades based on their increasing share of the waitlist (Figure 4). Several policy components were predicted to lead to a decrease in the number of deceased donor kidneys allocated to candidates over age 65. The early returns from the first 5 months with the new KAS confirm the predictions (Figure 5), with a slight decrease in the percentage of deceased donor kidneys allocated to candidates over age 65 (5). This is primarily due to longevity matching, in which the 20 percent of kidneys predicted to function the longest based on the KDPI are allocated first to candidates in the top 20 percent of expected posttransplant survival (EPTS) (6, 7). Candidates over the age of 55 are not included in the top 20 percent of candidates based on the EPTS. What cannot be simulated for the new KAS are changes in acceptance behavior. Whether older candidates (and transplant centers) increase their acceptance of kidneys with shorter predicted longevity, from donors with KDPI greater than 85, remains to be seen. This approach has worked well in the Eurotransplant program but has not been as widely accepted in the United States. Discard rates for kidneys with KPDI are still as high as 60 percent (Figure 6). Coming to terms with the risks and benefits of transplanting higher-risk kidneys (in terms of KDPI) into higher-risk elderly candidates will be critical in the coming years to maintain timely access to deceased donor kidneys for older transplant candidates. It also highlights the growing importance of living kidney donation, not just for the older population but for all candidates.

Figure 4. Recipient Age Distribution for US Kidney Transplants

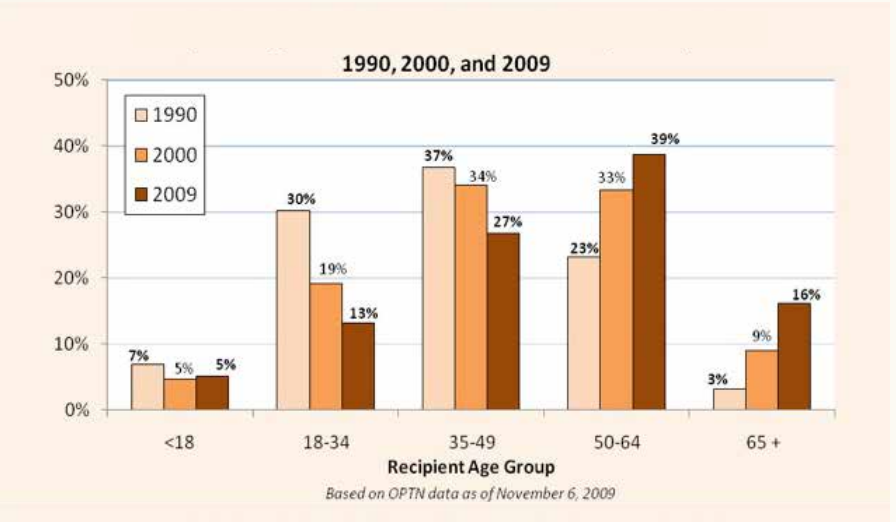


Figure 5. Changes in recipient characteristics following implementation of the new Kidney Allocation System

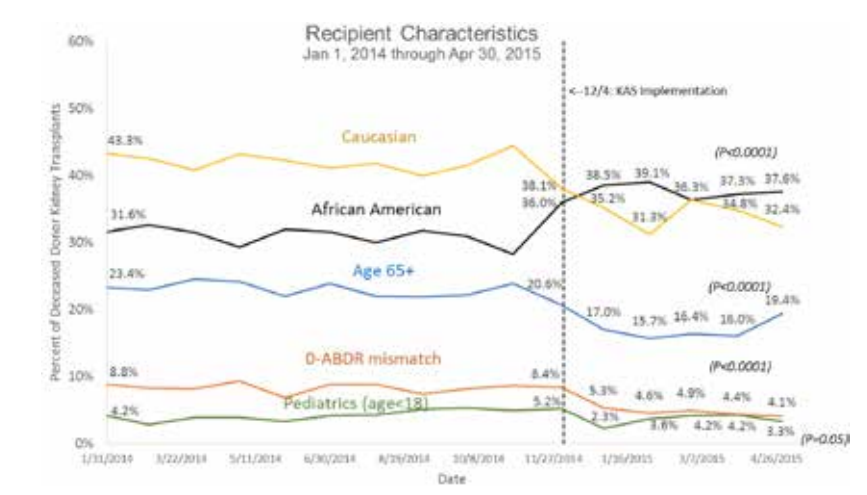
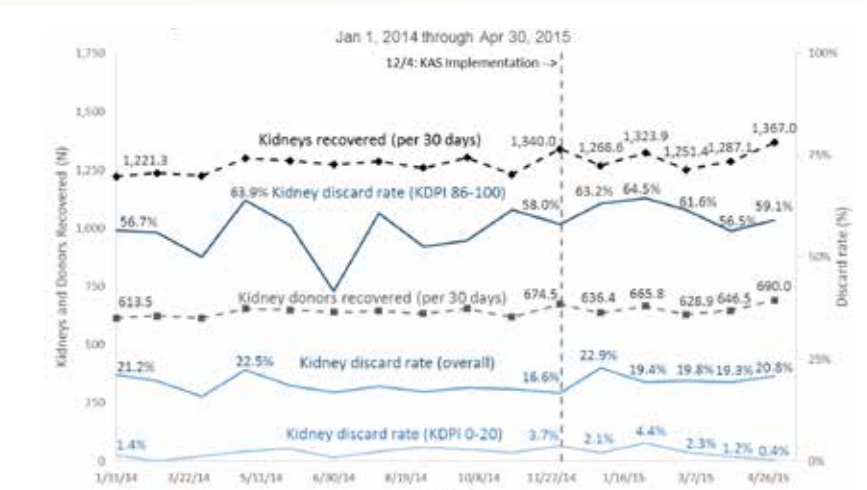


Figure 6. Changes in kidney discard rates following implementation of the New Kidney Allocation System

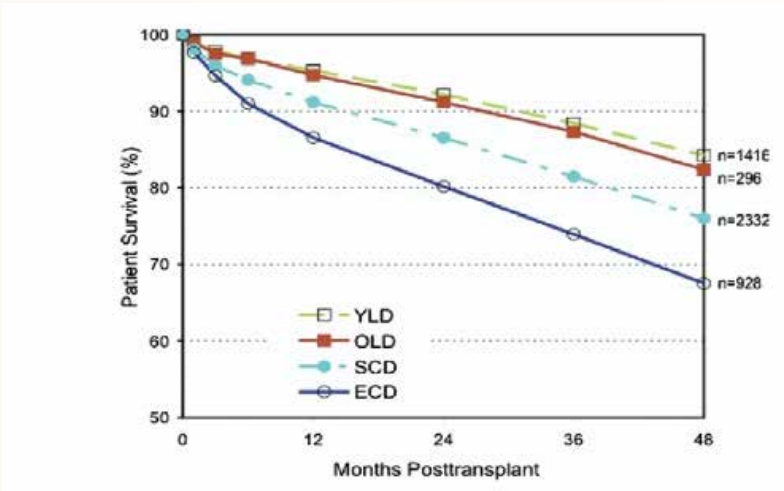


Living donation

Expanding living donor kidney transplantation is an effective way to shorten wait times and improve outcomes among elderly ESRD patients. One way to achieve this goal is to increase the number of older living kidney donors. Although donors older than 65 years constitute a very small percentage of all living kidney donors, over the past decade the number of older living kidney donors has increased (8). Published data suggest, not surprisingly, that transplants from younger living donors have better outcomes than those from older donors. However, a review of registry data by Gill et al. (9) focusing on 1133 transplants in recipients older than 60 years from relatively older living donors (>55 years) showed overall superior graft and patient survival compared with standard criteria donor (SCD) and expanded criteria donor (ECD) deceased donor transplants. When further stratification was made by donor age, allograft survival for recipients of kidneys from living donors 55 to 64 years old was similar to that achieved with younger living donor kidneys (Figure 7). Living donors aged 65 and older showed graft survival comparable with that of SCD transplants and superior to that of ECD transplants. Although long-term follow-up of donor outcomes is limited, there is no evidence to suggest that older donors have poorer outcomes than their younger counterparts, thus making pursuing living kidney donation relatively safe in selected elderly individuals.

Continued on page 22

Figure 7. Patient Survival Based on Donor Age and Type



Kidney Transplantation

Continued from page 21

Access to transplantation in a highly regulated environment

A new crisis is looming in the field of kidney transplantation. Transplant center outcomes (patient and graft survival) are being increasingly scrutinized—and for good reasons. We all want to improve quality and outcomes in our field. However, given the shortage of organs and the preponderance of candidates, the relative outcomes in different candidates are more often being taken into consideration as transplant programs decide their risk tolerance for transplantation. If a program takes an excessive risk that results in decreased patient or graft survival, it threatens the viability of that program. And increasingly, elderly candidates are the first to be passed over as candidates, as a result of the somewhat flawed methodology for correcting for expected risk (compared with observed risk) performed by the Scientific Registry of Transplant Recipients. It is in the interest of transplant centers to transplant patients with the best potential outcomes, or at least to perform transplantation in patients whose risks are well accounted for in the grading models. Age and cardiovascular disease are notoriously underaccounted for in outcomes modeling, making centers cautious to perform transplantation in such candidates. This grading system for transplant programs misaligns incentives with the global challenge to perform more transplantations. Until risk adjustment for transplant centers improves, patients on the margin will continue to have lower access to transplantation despite having the potential for improved outcomes compared with dialysis.

Management of immunosuppression in elderly transplant recipients

Aging affects the immune system in multiple ways and is associated with inflammation, altered innate immunity, and altered cell-mediated immunity (10, 11). The latter is characterized by decline in the production of naïve T cells, accumulation of senescent and exhausted T cells, and decline in T cell diversity. This suggests that the mechanisms governing rejection may differ in older and younger recipients. Delayed graft function, acute rejection with profound impact on graft function, and exaggerated chronic graft changes are more common in elderly transplant recipients. However, these patients are also more susceptible to infections and malignancies after transplantation, and this emphasizes the importance of a finely balanced immunosuppressive regimen. Many transplant centers use interleukin-2 receptor antagonists for induction over lymphocyte-depleting agents, along with maintaining lower drug levels for maintenance immunosuppression to achieve a favorable risk-to-benefit profile. Other factors to be considered in the treatment of elderly kidney transplant recipients include drug interactions in the setting of polypharmacy and physiological impact of age on drug pharmacokinetics, pharmacodynamics, and adverse effects.

Summary

We have an aging ESRD population that presents specific challenges to the transplant community. There are less exaggerated differences in survival when transplantation is compared with dialysis in older patients. Yet, transplantation still may be the preferred therapy for ESRD in many elderly patients. Determining candidacy with objective measures of frailty and disability are crucial to supplement the traditional listing criteria. Maintaining access for older candidates is a looming issue that will need to be resolved at the federal level, but nephrologists must continue to advocate for their patients in this arena. Last, the approach to immunosuppression must be carefully tailored to the aging immune system, to avoid toxicity and maximize efficacy.

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End-of-Life Decision Making

By Vanessa Grubbs

"If you really want to do something, you'll find a way. If you don't, you'll find an excuse."
—Jim Rohn, American entrepreneur, author, and motivational speaker

Arguably, the biggest problem facing end-of-life decision making in elderly patients with advanced and end stage renal disease is that conversations about the end of life simply don't happen often enough. In one survey of dialysis patients, fewer than 10 percent reported having a conversation about end-of-life issues with their nephrologist in the past year. Moreover, fewer than 10 percent reported that any physician had ever discussed prognosis with them (1). This despite evidence that patients and family members want to be given information about life expectancy even if the prognosis is poor, and those engaged in shared, informed decision making are more likely to make decisions about renal replacement therapy and end-of-life care consistent with their personal values—often resulting in preferences for less aggressive care and greater use of conservative management (2–4).

One explanation often given for the dearth of end-of-life conversations is nephrologists' lack of training to have them. In a 2003 survey, nephrology fellows reported that they had received little training on end-of-life issues and felt less prepared to take care of dialysis patients at the end of life compared with other practice skills (5). Ten years later, a similar survey of nephrology fellows gave nearly identical results (6). Without meaningful incorporation of palliative care into nephrology training, another survey in 2023 would undoubtedly yield nearly the same results yet again. Perhaps nephrology fellowships have not made significant progress in this area because the nephrologists doing the training aren't comfortable teaching the subject. Therefore, the key to true reform of nephrology training may lie in a requirement that practicing nephrologists obtain training in palliative and end-of-life care, similar to how many states in this country began requiring continuing medical education in pain management for licensure in the early 2000s.

It is also commonly assumed by nephrologists that there is not enough time to discuss end-of-life issues with patients and families. There is no way around the reality that talking through how we hope to live out the remainder of our lives usually takes time, often repeatedly. Many nephrologists turn to dialysis social workers and nursing staff to have these conversations, but patients and families prefer to have end-of-life discussions with their doctors (1, 3). Although dialysis social workers and nursing staff may be tasked with following up with end-of-life discussions, the assignment of health care proxies, and the completion of living wills, nephrologists must remain primarily responsible for discussing prognosis and goals of care with patients and families. Improved expertise in the area would allow nephrologists to facilitate such discussions with greater ease and efficiency. Perhaps a system-level realignment of financial incentives for achieving metrics, such as meaningful elicitation of patient goals and use of appropriate services near the end of life, would allow nephrologists to restructure their time allocation.

Finally, a lack of prognostic certainty is also considered a major barrier to end-of-life conversations. It is not surprising that we nephrologists are uncomfortable with diagnostic uncertainty, given that the field is rife with equations. There are equations to calculate deficits of free water, bicarbonate, and sodium; more equations to calculate fractional excretion of sodium and urea; and still more to calculate creatinine clearance and glomerular filtration. Although tools to estimate prognosis among dialysis patients exist and those to estimate prognosis among patients with advanced kidney disease are in development, without a crystal ball it is doubtful that any tool will ever have enough precision for clinicians to feel assured of accuracy for any patient before them. But compared with the vast majority of patients and families who have only their "n of 1" experience with illness, our clinical knowledge and experiences with similar patients is invaluable and should be shared.

The penalty for not having end-of-life conversations is that the default for our elderly patients is intensive care patterns focused on prolonging life, when survival alone may not be the only thing that matters to them. Currently, many older adults in the United States being treated with maintenance dialysis continue to receive aggressive care focused on life prolongation toward the end of their lives. Almost half (45 percent) of older dialysis patients in the United States die in a hospital setting, compared with 35 percent of older patients with other severe chronic illness, including congestive heart failure, advanced liver disease, dementia, and chronic obstructive pulmonary disease (7). The rates of hospitalization (76 percent) and intensive care unit (ICU) admission (49 percent) during the final month of life are also substantially higher than those reported for other older Medicare beneficiaries, including those with cancer (of whom 61 percent are hospitalized and 24 percent are admitted to an ICU) and heart failure (of whom 64 percent are hospitalized and 19 percent are admitted to an ICU). Additionally, older dialysis patients spend twice as many days in the hospital during the last month of life, compared with older patients with cancer (9.8 versus 5.1 days) and are three times more likely to undergo intensive procedures like mechanical ventilation, feeding tube placement, and cardiopulmonary resuscitation (29 percent versus 9 percent). By contrast, the rates of palliative care and hospice use among dialysis patients at the end of life are extremely low (7). Compared with hospice use in patients with terminal cancer (55 percent) and heart failure (39 percent), the use of hospice is only 20 percent among dialysis patients and is often initiated only within the last days of life (7–9).

Inasmuch as dialysis may be life-saving treatment in many circumstances, it seems to lull us—clinicians, patients, and families alike—into a false sense that acute events are temporary, when the truth is that dialysis cannot change the reality that the trajectory of kidney failure is continuous and is characterized by acute illnesses and setbacks where recovery is never back to baseline functional status and ends in death (Figure 1) (10). Perhaps if we could embrace this fact we could take action to help our patients prepare for the inevitability of death with the same vigor that we apply to helping them prepare for renal replacement therapy.

More than 1 in 5 of our patients die every year. The onus is on us to move beyond pointing out the reasons why we fail to act in ways that ensure these deaths are aligned with our patients' values.

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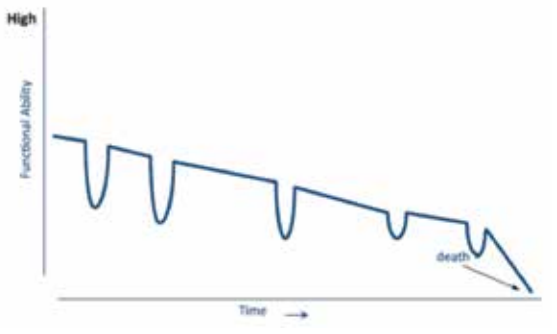
Figure 1. Illness trajectory of kidney failure—despite dialysis



Adapted from reference 10

Practice Pointers

Shared Decision Making and Ethical Issues in Dialysis

By Alvin H. Moss

Alvin H. Moss, MD, FACP

KN: Dr. Moss, please tell us something about yourself and how you got interested in the broad topic of medical ethics, particularly as it applies to dialysis patients.

Dr. Moss: I have been a nephrologist for 35 years. After just a few years, I became a dialysis unit medical director. The first patient I encountered after this appointment piqued my interest in the ethics of dialysis. Since that initial patient I have taken intensive courses in medical ethics at the Kennedy Institute of Ethics of Georgetown University and spent a sabbatical year at the University of Chicago's MacLean Center for Clinical Medical Ethics. I have served as the ethics series editor for the *Clinical Journal of the American Society of Nephrology* since 2009.

I was minding my own business making dialysis rounds as a junior nephrologist when one of the healthiest patients in our dialysis unit said to me, "Dr. Moss, I want to stop dialysis. This is no type of life." I was shocked. I did not know whether he ethically and legally could stop dialysis. I had not been trained in how to respond to such a request by a dialysis patient. This patient triggered my interest to study this and many other ethical issues in dialysis.

KN: What are the most common ethical dilemmas faced by most clinicians today? Is this different or similar compared with yesteryear, and how?

Dr. Moss: The two broad themes of common ethical dilemmas in dialysis relate to decisions about starting, continuing, and stopping dialysis and to determining how to respond to the behavior of "difficult and disruptive" patients. The same issues have been the most troubling for two decades, but the difficulties raised by them have changed. For example, decision making about having an older patient (>75 years old) with significant comorbidities begin dialysis is better informed because now many studies have identified the limitations of giving such patients dialysis. Nonetheless, there are still the psychological and social issues raised by families who do not want their loved ones to die. The American Society of Nephrology in its Choosing Wisely campaign identified shared decision making in such situations as one of the top five important questions that nephrologists need to discuss with patients and families. Based on cases I hear about from all over the country, I also get the sense that disruptive and difficult patients are more violent and threatening to dialysis staff than they used to be 10 to 20 years ago. Sadly, every year or two we hear of a dialysis nurse who was murdered by a patient.

KN: Please give us a summary of your work on *Shared Decision Making in the Appropriate Initiation of and Withdrawal from Dialysis.*

Dr. Moss: This clinical practice guideline was developed by use of the approach recommended by the Institute of Medicine, is evidence based, and makes 10 recommendations about the treatment of adult patients with acute kidney injury, chronic kidney disease (CKD), and ESRD. The Institute of Medicine defines clinical practice guidelines as "statements that include recommendations, intended to optimize patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options." With each recommendation in the *Shared Decision Making* guideline, there is a rationale with a literature review and also suggested strategies or resources that the nephrologist can use to implement the recommendation. There is a tool kit section in the guideline with helpful resources to calculate a comorbidity score, assess pain and symptoms, rate malnutrition, communicate with patients and families about their goals for treatment, and respond with a systematic process to a decision about whether to withhold or withdraw dialysis. This guideline has been recognized as the international gold standard for dialysis decision making. Unfortunately, in surveys of dialysis personnel in the United States, only about 15 percent are aware of and use the guideline. Ironically, when dialysis personnel are asked what would most help them in providing palliative care in their dialysis unit, they identify as their number one most helpful thing a clinical practice guideline just like the *Shared Decision Making* guideline. The guideline is now available for free for download from the Renal Physicians Association website at http://www.renalmd.org/catalogue-item.aspx?id=682.

KN: As you know, we live in the age of technology, the age of social media, the age of the Internet. How has this influenced the minds of present-day clinicians in dealing with ethical issues?

Dr. Moss: I am afraid that the technological imperative "if you can dialyze a patient, you must dialyze the patient" and the influence of social media have led nephrologists to think they are ethically obligated to dialyze everyone. Nephrologists are still under the Hippocratic maxim "to be of benefit and do no harm." There is accumulating evidence that dialysis is not likely to benefit certain patients, particularly those over the age of 75 with significant comorbidities. Clinicians need to be more aware of the recent literature and the *Shared Decision Making* guideline, and know how to apply the ethical principles in the guideline to decisions with patients and families when dialysis is not medically indicated.

KN: Please briefly describe one or two unforgettable patients you have been involved with, and share with us your knowledge and experience in handling their cases.

Dr. Moss: I alluded to the first patient above. He was a 54-year-old gentleman with membranous glomerulonephritis but no other significant medical problems. He had a great arteriovenous fistula, and his dialysis treatments were smooth. He had the best set of laboratory results in the unit. When he asked to stop dialysis, I could not believe it. I did not know much then about ethical issues in dialysis. I punted and said to him, "How about if we both think about it for a month, and then if you still feel that way we can talk about it some more." Fortunately, at the end of the month he did not bring it up, and I did not either. The following spring he said to me, "Doc, I'm really glad that you didn't listen to me last fall. I just really enjoyed putting in my garden, and I'm looking forward to a great crop this summer." I thought nothing more about it until November of that year, when he made the same request to me about stopping dialysis. It was only at that point that I realized that he had seasonal affective disorder. With appropriate treatment, he continued with dialysis for many more years! He did not want a transplant because he was doing so well with dialysis.

The second patient was a 75-year-old woman who had severe chronic lung disease from berylliosis. It was occupationally acquired from working in a lighting plant in a nearby West Virginia town. She wore oxygen 24 hours a day and had recurrent problems with bronchitis and pneumonia. When she experienced advanced CKD, I recommended against dialysis because I was afraid that between the dialysis and the lung disease her quality of life would be very poor. She told me that she still had things to live for and that she wanted to give dialysis a try. Against my better judgment at the time, I had an arteriovenous fistula placed, and when ESRD developed she started dialysis. Fortunately I had a long discussion with her about the circumstances under which she would want to stop dialysis. Three years later she had a massive stroke, which left her in a coma, and I discussed with her family that she would no longer want to continue dialysis in her present state. The family agreed, and the decision to stop dialysis was made without conflict.

These cases taught me the importance of learning the patient's perspective and identifying patients' goals for treatment. Advance care planning is very important to conduct with patients to learn their wishes for treatment now and in the future. Once I had talked to that first patient, he had many reasons for wanting to live. Both cases highlight the importance of having a systematic process for addressing the decision to stop dialysis.

KN: What is your perspective on hospice in the dialysis population?

Dr. Moss: Hospice is for patients who have 6 months or less to live if their disease process takes its normal course. In my experience, many dialysis patients want to continue dialysis, but they also want better pain and symptom management to improve their quality of life. It would be ideal if patients did not need terminal diagnoses unrelated to their kidney disease to qualify for hospice and yet still continue dialysis. Concurrent dialysis and hospice would best meet the needs of these patients for meticulous pain and symptom management, comprehensive advance care planning, and psychological and social support for the patient and the family. I hope in my lifetime I will see a change in Medicare coverage to allow concurrent hospice and dialysis when the terminal diagnosis is related to kidney disease. I suspect that patients and families will report greater satisfaction and the cost of care will decrease because patients will have fewer hospitalizations.

KN: One common question I encounter in clinical practice is when a family member asks, "Isn't my relative too old for dialysis?" Certainly, I understand that the approach must be individualized, but can you give us practice pointers on how to handle this question?

Dr. Moss: You are right to state that the approach must be individualized. The most important factor in determining the survival of a patient on dialysis is not age but the severity of the patient's comorbidities. Evidence over the past decade points to the following four factors as being statistically significant independent predictors of poor prognosis for dialysis patients: multiple significant comorbidities, particularly dementia and peripheral arterial disease; poor nutritional status; poor functional status; and age over 75. If the patient has two or more of these factors, the likelihood that dialysis will benefit the patient is questionable. Research findings now allow us to use a highly accurate validated integrated prognostic model that can be used for free online to predict 6-month and 12-month survival for hemodialysis patients (http://touchcalc.com/calculators/sq).

To use the website, nephrologists enter the patient's age, serum albumin, the nephrologist's response to the surprise question "Would I be surprised if this patient died in the next 6 months?" and whether or not the patient has dementia or peripheral arterial disease. The website then estimates the likely 6-month, 12-month, and 18-month survival times. This online calculator is based on research involving a thousand patients, with 500 patients in a derivation sample for the model and 500 patients in a validation sample. The C-statistic for accuracy of this integrated prognostic model was 0.8. This is as good a C-statistic for a prognostic model as is available for any other chronic disease. I would recommend that nephrologists use the integrated prognostic model and the recommendations in the *Shared Decision Making* clinical practice guideline to conduct individualized, patient-centered decision making about dialysis with patients and their families (see sidebar for *Shared Decision Making* guideline recommendations).

KN: What is palliative dialysis? Can it be defined?

Dr. Moss: Palliative dialysis involves a transition from a conventional disease-oriented focus on dialysis as rehabilitative treatment to an approach to dialysis patient care in which the treatment the patient receives is aligned with the patient's preferences for comfort and dignity over prolonged survival.

The goal of palliative dialysis is to improve the patient's quality of life, to reduce the burden of symptoms, and to enable the patient to live as long and as well as possible (the way the patient defines it) and to die gently. Patients receiving palliative dialysis likely will want limitations on other treatments. For example, likely they would not want intubation and mechanical intervention in an intensive care unit, they would not want CPR, and they would not want vasopressors used in the event of shock.

KN: Do you think that most clinicians today are more cognizant of this concept? Why or why not?

Dr. Moss: I believe only a minority of nephrology clinicians are aware of this concept. This concept is presented in the *Shared Decision Making* clinical practice guideline, which has not been well read. Several articles published on palliative dialysis have been published since that time, and I think palliative dialysis is still largely misunderstood.

KN: Do you think many of our colleagues opt not to discuss advance care planning with our future potential dialysis patients? Why or why not?

Dr. Moss: Most nephrologists have not been trained in how to conduct advance care planning conversations and therefore do not feel comfortable doing so. More and more it has been realized that nephrologists can team with a nurse practitioner, a nurse, or a social worker in the dialysis unit to facilitate advance care planning. The nephrologist does not need to conduct the whole discussion but needs to provide information to the patient, family, and other dialysis personnel about the patient's present medical condition, prognosis, and likely future medical complications. In surveys, dialysis patients report that they want to participate in advance care planning discussions. These discussions are important because they are the only way nephrologists and other nephrology clinicians will be able to identify and respect patients' future treatment wishes.

KN: Do you have any final practice advice to our colleagues, young and old, on this issue?

Dr. Moss: I recommend that everyone reading this article and download, save, read, and refer to the *Shared Decision Making in the Appropriate Initiation of and Withdrawal from Dialysis*, 2nd edition, clinical practice guideline as needed when clinical situations arise. The guideline contains strategies for implementing each recommendation in patient care. In addition, I would refer colleagues to the Coalition for Supportive Care of Kidney Patients website, www.kidneysuppportivecare.org. This website has many resources that can aid nephrology clinicians in learning about pain and symptom management, advance care planning, and other aspects of supportive care for the kidney patient. It includes an up-to-date bibliography of articles published about kidney palliative care. Third, I would recommend to my colleagues that they download the free iTunes app made possible by the Renal Physicians Association with a grant from DaVita. The app contains workflow for renal palliative care for patients before dialysis, during dialysis, and as dialysis is stopped. It contains links to the above websites and to many helpful palliative care resources for kidney patients. Finally, I would recommend to my colleagues that they identify a palliative care physician in the community with whom they can collaborate in the care of more complex patients. It is unreasonable to expect that nephrology clinicians have the time and the skills needed to treat all the issues raised by a dialysis center full of patients. Palliative care clinicians can assist nephrologists even before the patient is thought to be terminally ill. There are strong collaborations between nephrologists and palliative care clinicians throughout the country, and the patients and the clinicians benefit from this teamwork.

Alvin H. Moss, MD, FACP, is the ethics series editor of the Clinical Journal of the American Society of Nephrology.

Recommendations in the *Shared Decision Making in the Appropriate Initiation of and Withdrawal from Dialysis*, 2nd edition clinical practice guideline

Establishing a shared decision making relationship
Recommendation No. 1
Develop a physician–patient relationship for shared decision making.

Informing patients
Recommendation No. 2
Fully inform AKI, stage 4 and 5 CKD, and ESRD patients about their diagnosis, prognosis, and all treatment options.

Recommendation No. 3
Give all patients with AKI, stage 5 CKD, or ESRD an estimate of prognosis specific to their overall condition.

Facilitating advance care planning
Recommendation No. 4
Institute advance care planning.
Make a decision to not initiate or to discontinue dialysis.

Recommendation No. 5
If appropriate, forgo (withhold initiating or withdraw ongoing) dialysis for patients with AKI, CKD, or ESRD in certain well-defined situations. Medical management incorporating palliative care is an integral part of the decision to forgo dialysis in AKI, CKD, or ESRD, and attention to a patient's comfort and quality of life while dying should be addressed directly or managed by palliative care consultation and referral to a hospice program (see Recommendation No. 9 on palliative care services).

Recommendation No. 6
Consider forgoing dialysis for AKI, CKD, or ESRD patients who have a very poor prognosis or for whom dialysis cannot be provided safely.

Resolving conflicts about what dialysis decisions to make
Recommendation No. 7
Consider a time-limited trial of dialysis for patients who require dialysis but who have an uncertain prognosis, or for whom a consensus cannot be reached about providing dialysis.

Recommendation No. 8
Establish a systematic due process approach for conflict resolution if there is disagreement about what decision should be made with regard to dialysis.

Providing effective palliative care
Recommendation No. 9
To improve patient-centered outcomes, offer palliative care services and interventions to all AKI, CKD, and ESRD patients who suffer from the burdens of their disease.

Recommendation No. 10
Use a systematic approach to communicate about diagnosis, prognosis, treatment options, and goals of care.

Abbreviations: AKI = acute kidney injury; CKD = chronic kidney disease; ESRD = end stage renal disease.

Findings

Authors Challenge Memory-Based Dietary Assessments

Dietary recall, food frequency questionnaires, and other memory-based dietary assessment methods (M-BMs) are "pseudoscientific" and shouldn't be used to set dietary guidelines and policies, concludes a special article in *Mayo Clinic Proceedings*.

Edward Archer, PhD, of the University of Alabama at Birmingham and colleagues evaluated the validity of using M-BMs for nutrition surveillance and epidemiologic nutrition research. Their critique focuses on the "What We Eat in America" and National Health and Nutrition Examination Surveys (WWEIA/NHANES), which relied on 24-hour recall and food-frequency questionnaires to assess diet.

The authors cite "many decades of evidence demonstrating that M-BMs have severe, intractable systematic biases that render the data implausible and, therefore, invalid." Not only is it "indisputably false" that human memory can accurately or precisely reproduce past consumption, but M-BM protocols mimic procedures designed to produce false recall, they write.

The memories on which M-BM data are based cannot be independently confirmed or refuted; "as such, these data are pseudoscientific and inadmissible in scientific research," according to the authors. They add that failure to measure and control for physical activity, cardiorespiratory fitness, and other confounders leads to equivocal inferences about the relationship between diet and health.

On the basis of this "overwhelming evidence," Archer and colleagues conclude, "M-BM data cannot be used to inform national dietary guidelines." They believe that continued funding of projects using these methods, such as WWEIA/NHANES, "constitutes an unscientific and major misuse of research resources" [Archer E, et al. The inadmissibility of What We Eat in America and NHANES dietary data in nutrition and obesity research and the scientific formulation of national dietary guidelines. *Mayo Clin Proc* 2015; doi: 10.1016/j.mayocp.2015.04.009].

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Industry Spotlight

Dialysate Concentrate Recalled

In July 2015, Fresenius issued a voluntary recall of more than 1.8 million 6.4-L bottles of NaturaLyte Liquid Bicarbonate Concentrate (see FDA website for details about the recalled units). The concentrate is formulated for use with a three-stream hemodialysis machine that is calibrated for acid and bicarbonate concentrates, the FDA noted.

NaturaLyte is also making news on some legal websites for a class-action suit against the manufacturer, alleging that the product, along with a different Fresenius dialysate product called GranuFlo, contributed to harmful and/or fatal side effects such as cardiac arrhythmia and low blood pressure. On July 1, 2015, the latest case was filed in Mississippi. The case joins other cases included in previously established multidistrict litigation (MDL No. 2428, In Re: Fresenius Granuflo/Naturalyte Dialysate Products Liability Litigation), created to expedite trials for related lawsuits.

The New York Times reported in 2012 about questions regarding Fresenius failure to warn non-Fresenius dialysis clinics about possible adverse cardiac events with GranuFlo use. The events might be brought on during dialysis related to a build-up of bicarbonate in patients, the *Times* reported. Clinics began to monitor blood levels for problems, and the product was relabeled.

In June, Fresenius Medical Care Renal Therapies Group began a voluntary recall of Crit-Line blood chambers used in hemodialysis because of product leakage problems. The recall involved 22.6 million

products sold in the United States, Ireland, Spain, Slovenia, Great Britain, the Netherlands, Norway, Mexico, Egypt, and the Czech Republic.

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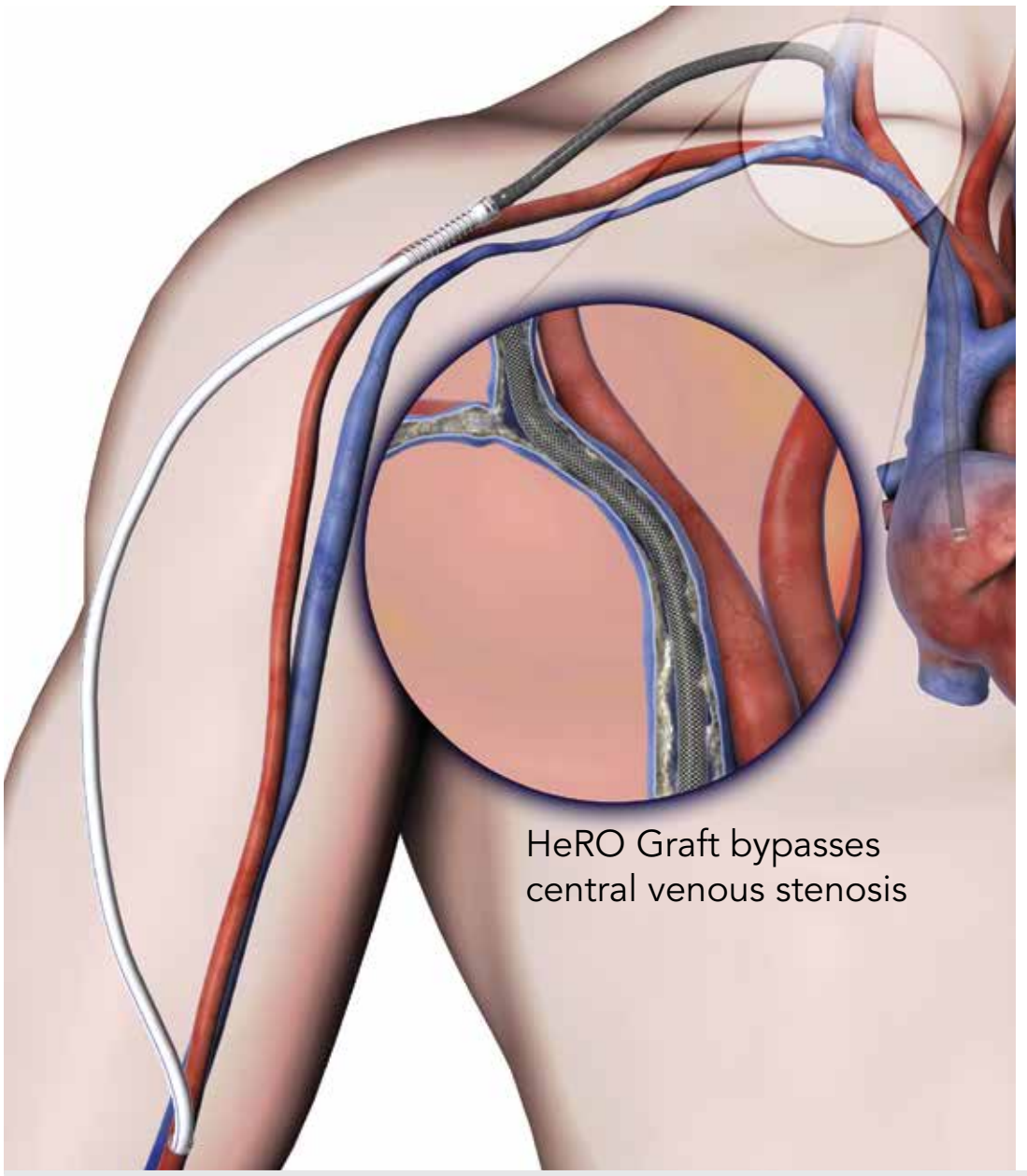

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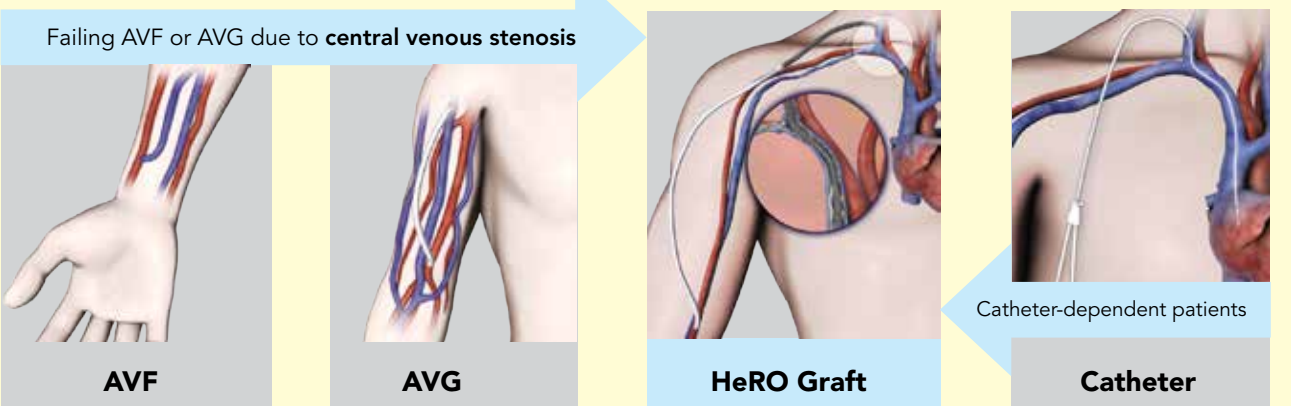
Treatment Algorithm



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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.

Indications for Use: The HeRO Graft is indicated for end stage renal disease patients on hemodialysis who have exhausted all other access options. See Instructions for Use for full indication, contraindication and caution statements. Rx only.

HeRO Graft is classified by the FDA as a vascular graft prosthesis.

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