Findings from a new study could lead to better diagnosis and treatment of patients with immunoglobulin A (IgA) nephropathy, one of the most common diseases of the kidney. The results, published in the Journal of the American Society of Nephrology, indicate that increasing blood levels of certain autoantigens and autoantibodies may act as warning signs that a patient’s disease is worsening and that aggressive interventions are needed.

The findings also support a predominant role of an autoimmune mechanism in the pathogenesis of IgA nephropathy, which remains partly unsolved.

“The intimate details of the cascade of events leading eventually to destruction of the kidneys are complex and still puzzling,” said first author Francois Berthoux, MD, of the University Hospital of Saint-Etienne, in France.

Assessing disease severity
Patients with IgA nephropathy, a condition that was first described in 1968, have increased serum levels of IgA1 that is galactose deficient. In the absence of galactose, terminal N-acetylgalactosamine residues are exposed. Consequently, such IgA1 molecules are presented as autoantigens, and IgG or IgA glycan-specific autoantibodies recognize them to form immune complexes that circulate in the blood and can settle in the kidneys. These events can damage the kidneys, which subsequently leak blood and protein in the urine. IgA nephropathy can lead to high blood pressure, swelling, and, in some cases, kidney failure.

At the time of diagnosis, it remains difficult to predict the long-term clinical outcome for patients with IgA nephropathy. “The disease is clinically heterogeneous, with 20 percent to 30 percent of patients progressing to chronic kidney disease,” said Ian Roberts, MD, of the department of cellular pathology at John Radcliffe Hospital, in England, “The challenge is to identify those patients who will progress and could potentially benefit from immunosuppressive ther-

Physician Quality Reporting System: Incentive Today, Gone Tomorrow
By Rachel Shaffer
Since 2007, physicians and other eligible health professionals have been eligible to receive bonus Medicare payments for voluntarily reporting data to the Physician Quality Reporting System (PQRS) program. Starting in 2013, that program will no longer be voluntary, and every physician and other health professional with a National Provider Identifier (NPI) number should be aware of important changes to the PQRS that will affect their Medicare payments (Table 1).

The PQRS is a congressionally mandated program operated by the Centers for Medicare & Medicaid Services (CMS). The Tax Relief and Health Care Act of 2006 first authorized the incentive program, and the Medicare Improvement for Patients and Providers Act of 2008 made it permanent. The PQRS is not entirely unique. CMS maintains several quality measurement program initiatives to help it monitor the quality of care in different environments—including the End-Stage Renal Disease Quality Incentive Program for dialysis facilities—and holds that such quality initiatives aim to give providers and patients information that improves
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Physician Quality Reporting System

Continued from page 1

the overall delivery and coordination of care. In 2009, more than 210,000 eligible professionals voluntarily submitted data to the PQRS and received an average bonus payment of $2000.

Payment penalties in 2015

Currently, there is no requirement to participate in PQRS. Physicians and other eligible health professionals may receive a 0.5 percent bonus payment for submitting data to the PQRS in 2012. In earlier years of the PQRS program CMS provided up to a 2 percent bonus for reporting data, but has been decreasing that amount steadily. Providers who participate in 2012, 2013, and 2014 will receive a 0.5 percent bonus payment. Notably, providers may report data for 2012 to CMS through March 2013 to receive a bonus payment for 2012. Providers may submit data to CMS via claims, registries, or electronic health records. See the sidebar—and future issues of *Kidney News*—to learn how ASN is preparing to help you report your data efficiently and accurately via a registry in the coming weeks.

However, starting in 2015 CMS will reduce payments to eligible health professionals who did not successfully participate in the PQRS in 2013 (Table 2). Eligible health professionals will receive a 1.5 percent payment penalty in 2015 (based on lack of participation or unsuccessful participation in 2013) and a 2 percent payment penalty every year thereafter (based on lack of participation or unsuccessful participation 2 years prior). CMS will apply the PQRS penalty by adjusting providers’ Medicare Part B physician fee schedule. Consequently, it will be imperative for any provider with an NPI number to successfully participate in the PQRS program in 2013 in order to avoid payment reductions in 2015.

Reporting options: individual or measure groups

Eligible professionals may report on either individual measures or report “measure groups” of similar measures each year. Providers reporting individual measures through a registry—such as those for the Physician Quality Reporting System (PQRS) program—will receive the maximum bonus payments. Providers using registries to report measure groups will receive smaller bonus payments. Providers who choose to report individual measures on a registry will receive a 1.5 percent bonus payment for 2015 (Table 2). Providers who choose to report measure groups will receive a 1 percent bonus payment for 2015 (Table 2). Providers who choose to report individual measures through a registry will receive a 1.5 percent bonus payment for 2015 (Table 2). Providers who choose to report measure groups will receive a 1 percent bonus payment for 2015 (Table 2). Providers who choose to report individual measures through a registry will receive a 1.5 percent bonus payment for 2015 (Table 2). Providers who choose to report measure groups will receive a 1 percent bonus payment for 2015 (Table 2). Providers who choose to report individual measures through a registry will receive a 1.5 percent bonus payment for 2015 (Table 2). Providers who choose to report measure groups will receive a 1 percent bonus payment for 2015 (Table 2). Providers who choose to report individual measures through a registry will receive a 1.5 percent bonus payment for 2015 (Table 2). Providers who choose to report measure groups will receive a 1 percent bonus payment for 2015 (Table 2). Providers who choose to report individual measures through a registry will receive a 1.5 percent bonus payment for 2015 (Table 2). Providers who choose to report measure groups will receive a 1 percent bonus payment for 2015 (Table 2). Providers who choose to report individual measures through a registry will receive a 1.5 percent bonus payment for 2015 (Table 2). Providers who choose to report measure groups will receive a 1 percent bonus payment for 2015 (Table 2).

Table 1. Professionals eligible to participate in Physician Quality Reporting System

<table>
<thead>
<tr>
<th>Category</th>
<th>Professionals eligible to participate in Physician Quality Reporting System</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Practitioners</td>
<td>Physician Assistant&lt;br&gt;Nurse Practitioner&lt;br&gt;Clinical Nurse Specialist&lt;br&gt;Certified Registered Nurse Anesthetist (and Anesthesiologist Assistant)&lt;br&gt;Certified Nurse Midwife&lt;br&gt;Clinical Social Worker&lt;br&gt;Clinical Psychologist&lt;br&gt;Registered Dietician&lt;br&gt;Nutrition Professional&lt;br&gt;Audiologist</td>
</tr>
<tr>
<td>3. Therapists</td>
<td>Physical Therapist&lt;br&gt;Occupational Therapist&lt;br&gt;Qualifed Speech-Language Therapist</td>
</tr>
</tbody>
</table>

Table 2. Percent Medicare payment bonus/reductions based on PQRS participation

<table>
<thead>
<tr>
<th>Year</th>
<th>Successful PQRS Participation</th>
<th>Successful PQRS Participation + Extra MOC</th>
<th>No/Unsuccessful PQRS Participation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>+2.0%</td>
<td>—</td>
<td>No change</td>
</tr>
<tr>
<td>2011</td>
<td>+1.0%</td>
<td>+1.5%</td>
<td>No change</td>
</tr>
<tr>
<td>2012</td>
<td>+0.5%</td>
<td>+1.0%</td>
<td>No change</td>
</tr>
<tr>
<td>2013</td>
<td>+0.5%</td>
<td>+1.0%</td>
<td>No change in 2013 Based on 2013 reporting –1.5%</td>
</tr>
<tr>
<td>2014</td>
<td>+0.5%</td>
<td>+1.0%</td>
<td>No change in 2014 Based on 2014 reporting –2.0%</td>
</tr>
<tr>
<td>2015</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>2016 onward</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
</tbody>
</table>

Abbreviation: MOC = maintenance of certification
as the registry ASN will make available—must submit patient data for 80 percent or more of their patients on at least three individual measures to be considered “successful” participants. Providers reporting data for measure groups must submit patient data for at least 30 Medicare patients on one measure group to be considered “successful” participants. The tool ASN will make available will help collect and report data on either individual measures or measure groups directly to CMS.

For 2012 CMS maintains 208 quality measures and 22 measure groups in the PQRS. The measure group “Chronic Kidney Disease,” may be of particular interest to nephrologists. That measure is to be reported for patients aged 18 years and older with chronic kidney disease receiving office or other outpatient services and is comprised of the following measures:

- Influenza immunization
- Laboratory testing (lipid profile)
- Blood pressure management
- Plan of care—elevated hemoglobin for patients receiving erythropoiesis-stimulating agents

However, other measure groups such as “Diabetes Mellitus,” “Hypertension,” Cardiovascular Prevention,” and “Preventive Care,” may also be of interest to nephrologists.

**PQRS and Maintenance of Certification**

There is good news for physicians participating in the maintenance of certification process: they may qualify for an additional “PQRS MOC Incentive Program.” Physicians who successfully participate in the PQRS program and participate in a MOC program “more frequently” than is required to qualify or maintain board certification status are eligible for an additional 0.5% increase in Medicare reimbursement. Therefore, physicians who participate in the PQRS MOC in 2012, 2013, and 2014 may receive up to a 1% bonus. See www.asn-online.org/MOC for more information.

More support from ASN

As noted above and in the sidebar, ASN will be making a reporting tool available that is designed specifically for the nephrology health professional. Be on the lookout for more information and additional PQRS resources to come in the weeks ahead. For more information in the meantime, please contact education@asn-online.org.
IgA Nephropathy

Continued from page 1

IgA nephropathy is an acquired renal disease characterized by the presence of IgA deposits in the glomerular mesangium or in situ glomerular malformation. In the glomerular mesangium, IgA deposits may form immune complexes, which can lead to an inflammatory response and progressive renal damage. The severity of IgA nephropathy is partly based on clinical and histologic features in kidney biopsy specimens, which can help in the diagnosis and management of the disease.

**Better blood markers**

To look for blood markers that might provide a better assessment of disease severity, Berthoux, along with Jan Novak, MD, PhD, of the University of Alabama at Birmingham; Hiroshi Tominaga, MD, PhD, of Juntendo University, in Tokyo, Japan; and their colleagues studied blood samples from 97 patients with IgA nephropathy and compared them with samples from 60 individuals without the disease (30 healthy individuals and 30 with non-IgA nephropathy disease). In patients with IgA nephropathy, the analyses were performed on serum samples taken at the time of diagnostic biopsy. The average observation interval from the onset of clinical disease to the final event (dialysis or death) or last follow-up visit was 13.8 years, and from diagnosis by biopsy to final event or last follow-up visit, the interval was 7.3 years. Mean serum levels of total autoantigen (U/mL), normalized IgG autoantibody (OD/0.5 μg), and total IgA autoantibody (U/mL) were significantly higher in patients than in the combined control individuals. Blood levels of both IgA1 autoantigen and the IgG and IgA antibodies increased in a stepwise fashion according to the severity of patients’ disease. Also, patients with high blood levels of antibodies against IgA1 at the time of diagnosis had a higher risk of eventually needing dialysis and dying prematurely.

The alternative definition for progressive IgA nephropathy based on reduced estimated GFR was used, only the normalized IgG autoantibody discriminated the progressors from the nonprogressors. In addition, there was no correlation between sex or age at diagnosis or sampling and any of the serum biomarkers.

This was a first step, and in the future we have to refine these tests to check the impact of different treatments on these serum biomarkers, and to imagine new therapies with direct impacts on IgA1 or on the specific antibody responses against it,” said Berthoux. He and his coauthors wrote that their findings are “consistent with a multihit hypothesis for the disease mechanism of IgA nephropathy, wherein an increased serum level of autoantigen alone is not sufficient to induce renal injury; it must combine with autoantibodies either in the circulation to form immune complexes that deposit in the glomerular mesangium or in situ with galactose-deficient IgA1 already in the mesangium.”

The report offers a new risk factor that, if confirmed in additional studies, can serve as a marker for selecting patients to be aggressively treated.

“The international community of pathologists and nephrologists who worked on the Oxford classification of IgA nephropathy is highly interested in finding serologic markers that could be added on the pathologic score. These efforts will hopefully provide a clue for selecting IgA nephropathy patients to be treated or not and to modulate the intensity of treatment in the likely progressors,” said Rosanna Coppo, MD, who was not involved with the study and is the director of the nephropathy, dialysis and transplantation unit at Regina Margherita Children’s University Hospital in Turin, Italy. Her own work indicates that the nephrotoxicity of aberrantly glycosylated IgA1 in IgA nephropathy is enhanced in the presence of systemic signs of oxidative stress.

John Radcliffe Hospital’s Roberts, who also did not participate in the study, noted that the findings raise some important questions.

“It is unclear how the autoantibody levels change over time, and it remains to be ascertained whether levels correlate with clinical markers of activity in a longitudinal study. Another important area of future investigation is the link between autoantibody levels and histological activity in IgA nephropathy,” he said. •

Study coauthors include Lise Thibaudeau, MD, Nicolas Maillard, MD, PhD, Christophe Mariat, MD, PhD (University Hospital of Saint-Etienne, France); Hiroko Yamagawa MD, PhD; Yashuiko Tomino, MD, PhD (Juntendo University, Tokyo, Japan); and Bruce Julian, MD, PhD (University of Alabama at Birmingham).

Disclosures: The authors reported no financial disclosures.

The article, entitled “Serum autoantibodies specific for galactose-deficient IgA1 associate with disease progression in IgA nephropathy,” is available online at https://jasn.asnjournals.org; doi:10.1681/ASN.2012010055.

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INDICATION AND LIMITATIONS OF USE
OMONTYS® (peginesatide) Injection is indicated for the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis. OMONTYS is not indicated and is not recommended for use in patients with CKD not on dialysis, in patients receiving treatment for cancer and whose anemia is not due to CKD, or as a substitute for red blood cell (RBC) transfusions in patients who require immediate correction of anemia. OMONTYS has not been shown to improve symptoms, physical functioning, or health-related quality of life.

IMPORTANT SAFETY INFORMATION
WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE.

Chronic Kidney Disease:
• In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL.
• No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.
• Use the lowest OMONTYS dose sufficient to reduce the need for red blood cell (RBC) transfusions.

Contraindications
OMONTYS is contraindicated in patients with uncontrolled hypertension.

Warnings and Precautions
Increased mortality, myocardial infarction, stroke, and thromboembolism:
• Using ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit. Use caution in patients with coexistent cardiovascular disease and stroke. Patients with CKD and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular reactions and mortality than other patients. A rate of hemoglobin rise of >1 g/dL over 2 weeks may contribute to these risks.
• In controlled clinical trials of ESAs in patients with cancer, increased risk for death and serious adverse cardiovascular reactions was observed. These adverse reactions included myocardial infarction and stroke.
• In controlled clinical trials of ESAs, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery (CABG) and deep venous thrombosis (DVT) in patients undergoing orthopedic procedures.
• In 2 trials of OMONTYS, patients with CKD not on dialysis experienced increased specific cardiovascular events.

Increased mortality and/or increased risk of tumor progression or recurrence in patients with cancer:
The safety and efficacy of OMONTYS have not been established for use in patients with anemia due to cancer chemotherapy. OMONTYS is not indicated in patients with cancer receiving chemotherapy.

Hypertension: OMONTYS is contraindicated in patients with uncontrolled hypertension. Appropriately control hypertension prior to initiation of and during treatment with OMONTYS. Reduce or withhold OMONTYS if blood pressure becomes difficult to control. Advise patients of the importance of compliance with antihypertensive therapy and dietary restrictions.

Lack or loss of response to OMONTYS: For lack or loss of hemoglobin response to OMONTYS, initiate a search for causative factors. If typical causes of lack or loss of hemoglobin response are excluded, evaluate for antibodies to peginesatide.

Dialysis management: Patients receiving OMONTYS may require increased anticoagulation with heparin to prevent clotting of the extracorporeal circuit during hemodialysis.

Laboratory monitoring: Evaluate transferrin saturation and serum ferritin prior to and during OMONTYS treatment. Administer supplemental iron therapy when serum ferritin is less than 100 mcg/L or when serum transferrin saturation is less than 20%.

Adverse reactions
The most common adverse reactions in clinical studies in patients with CKD on dialysis treated with OMONTYS were dyspnea, diarrhea, nausea, cough, and arteriovenous fistula site complication.

Please see accompanying Brief Summary.
You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.
Estimates of the protein-to-creatinine ratio in spot urine samples may be of value in evaluating proteinuria in pregnant women with suspected pre-eclampsia, according to a meta-analysis in the *British Medical Journal*. The meta-analysis included data from 13 studies evaluating the urinary spot protein-to-creatinine ratio or albumin-to-creatinine ratio for the detection of significant proteinuria in pregnant women with hypertension. All studies provided data on 24-hour urinary protein excretion results or adverse pregnancy outcomes.

Studies evaluating the protein-to-creatinine ratio showed significant variation in threshold values and in estimated sensitivities and specificities. The optimum threshold values ranged between 0.30 and 0.35, on average. However, none of the threshold values had estimated

### Could Frailty Explain Higher Mortality with Early Dialysis?

A large majority of patients starting dialysis in the United States are in frail condition, which may be a factor in the increased mortality associated with dialysis initiation at higher estimated GFR (eGFR) levels, suggests a report in the *Archives of Internal Medicine*.

The study included 1576 patients initiating dialysis, identified through the Comprehensive Dialysis Study of the U.S. Renal Data System. On the basis of the presence of at least two of three criteria—slowness/weakness, exhaustion, and low physical activity—75 percent of patients were considered frail. Even among patients younger than 40, the rate of frailty at the start of dialysis was 63 percent.

In multivariate analysis, a higher estimated eGFR at the beginning of dialysis was independently associated with frailty (odds ratio 1.44 per 5 mL/min/1.73 m²). Frailty was also significantly associated with mortality (hazard ratio [HR] 1.57) and time to first hospitalization (HR 1.26).

Consistent with previous reports, higher eGFR at the start of dialysis was associated with increased mortality: HR 1.12 per 5 mL/min/1.73 m². However, the effects of frailty were accounted for, the association was no longer significant.

With the current trend toward earlier dialysis, lower eGFR when patients start dialysis has been linked to increased mortality. Frailty could be one factor affecting clinical decisions about starting dialysis. The new study finds that nearly three-fourths of patients meet the criteria for frailty at dialysis initiation.

Frailty is associated not only with higher eGFR at dialysis but also with a higher risk of death and hospitalization. The researchers call for further studies evaluating the effects of dialysis on overall health and functional status in frail patients. They add, “Compensatory efforts other than dialysis aimed to improve functional capacity in this population should also be considered.” (Boa Y, et al. Frailty, dialysis initiation, and mortality in end-stage renal disease. *Arch Intern Med* 2012; 172:1071–1077).

### Journal View

**Spot Urine Samples for Assessing Proteinuria in Suspected Pre-Eclampsia**

24-hour urinary protein excretion results or albumin-to-creatinine ratio may be of value in evaluating proteinuria in pregnant women with suspected pre-eclampsia. The meta-analysis included data from 13 studies evaluating the urinary spot protein-to-creatinine ratio or albumin-to-creatinine ratio for the detection of significant proteinuria in pregnant women with hypertension. All studies provided data on 24-hour urinary protein excretion results or adverse pregnancy outcomes.

Studies evaluating the protein-to-creatinine ratio showed significant variation in threshold values and in estimated sensitivities and specificities. The optimum threshold values ranged between 0.30 and 0.35, on average. However, none of the threshold values had estimated

### Table 2 Adverse Cardiovascular Outcomes in Randomized Controlled Trials Comparing Higher and Lower Hemoglobin Targets in Patients with CKD

<table>
<thead>
<tr>
<th>Time Period of Trial</th>
<th>NHS (N = 1265)</th>
<th>CHOR (N = 1432)</th>
<th>TREAT (N = 4038)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>1.19 (1.06 – 1.34)</td>
<td>1.07 (0.94 – 1.21)</td>
<td>1.03 (0.91 – 1.17)</td>
</tr>
<tr>
<td>MI, hospitalization</td>
<td>1.03 (0.90 – 1.17)</td>
<td>1.28 (1.06 – 1.56)</td>
<td>1.27 (1.04 – 1.54)</td>
</tr>
<tr>
<td>MI, mortality</td>
<td>1.04 (0.91 – 1.20)</td>
<td>1.34 (1.03 – 1.74)</td>
<td>1.48 (1.07 – 2.27)</td>
</tr>
<tr>
<td>MI, stroke</td>
<td>1.04 (0.91 – 1.20)</td>
<td>1.34 (1.03 – 1.74)</td>
<td>1.48 (1.07 – 2.27)</td>
</tr>
</tbody>
</table>

### Editorials

**Early Dialysis?**

Higher Mortality with 6 (odds ratio 1.44 per 5 mL/min/1.73 m²). was independently associated with frailty.

**Comprehensive Efforts Other Than Dialysis**

“Comprehensive efforts other than dialysis are necessary to lower mortality and avoid hospitalizations in patients with chronic kidney disease.” (Finkelstein F, et al. Comprehensive Efforts Other Than Dialysis to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT)).

**Conclusions**

**OMONTYS (peginesatide) Injection for Intravenous or Subcutaneous Use**

**INDICATIONS AND USAGE**

- **OMONTYS** is indicated for the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis.

**Limitations of Use**

- **OMONTYS** is not indicated and is not recommended for use:
  - In patients with CKD not on dialysis because of safety concerns in this population.
  - In patients receiving treatment for cancer and whose anemia is not due to CKD, because ESAs have shown harm in some settings and the benefit-risk factors for OMONTYS in this setting have not been evaluated.
  - As a substitute for RBC transfusions in patients who require immediate correction of anemia.

**CONTRAINDICATIONS**

**OMONTYS** is contraindicated in patients with:

- Uncontrolled hypertension (see Warnings and Precautions).

**WARNINGS AND PRECAUTIONS**

**Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism**

- In controlled clinical trials of other ESAs in patients with CKD comparing higher hemoglobin targets (13 – 14 g/dL) to lower targets (9 – 11 g/dL), see Table 1, increased risk of death, myocardial infarction, stroke, congestive heart failure, thrombosis of hemodialysis vascular access, and other thromboembolic events was observed in the higher target groups.

- In trials of ESAs to target a hemoglobin level of greater than 11 g/dL, increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit. Use caution in patients with consistent cardiovascular disease and stroke. Patients with CKD and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular reactions and mortality than other patients. A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may contribute to these risks.

- In controlled clinical trials of ESAs in patients with cancer, increased risk for death and serious adverse cardiovascular reactions was observed. These adverse reactions included myocardial infarction and stroke.

- In controlled clinical trials, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery (CABG) and deep venous thrombosis (DVT) was observed in patients undergoing orthopedic procedures. The design and overall results of 3 large trials comparing higher and lower hemoglobin targets are shown in Table 2 (Normal Hematocrit Study (NHS), Correction of Hemoglobin Outcomes in Renal Insufficiency (CHOR) and Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT)).

**Adverse Cardiovascular Outcomes in Randomized Controlled Trials**

**Population**

- Patients with CKD on dialysis with chronic kidney disease (CKD) in adult patients on dialysis.

**Hemoglobin Target**

- Higher, Lower

<table>
<thead>
<tr>
<th>Hemoglobin Target (g/dL)</th>
<th>Mortality, Lower vs. Higher (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.5 (11.0, 11.6)</td>
<td>1.34 (1.04 – 1.74)</td>
</tr>
<tr>
<td>13.0 (12.5, 13.6)</td>
<td>1.28 (1.06 – 1.56)</td>
</tr>
<tr>
<td>14.0 (13.5, 14.6)</td>
<td>1.27 (1.04 – 1.54)</td>
</tr>
</tbody>
</table>

**Primary Endpoint**

- All-cause mortality:
  - All-cause mortality, MI, hospitalization for CRF, or stroke
  - All-cause mortality, MI, myocardial ischemia, heart failure, and stroke

**Adverse Outcome for Higher Target Group**

- All-cause mortality

**Hazard Ratio or Relative Risk**

- 95% CI

<table>
<thead>
<tr>
<th>Hazard Ratio or Relative Risk</th>
<th>MI, mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.04 (0.94 – 1.17)</td>
<td>1.03 (1.04 – 1.54)</td>
</tr>
</tbody>
</table>

**Patients with Chronic Kidney Disease Not on Dialysis**

OMONTYS is not indicated and is not recommended for the treatment of anemia in patients with CKD who are not on dialysis.

A higher percentage of patients (22%) who received OMONTYS experienced a composite cardiovascular safety endpoint event compared to 17% who received darbepoetin alfa in two randomized, active-controlled, open-label, multi-center trials of 983 patients with anemia due to CKD who were not on dialysis. The trials had a pre-specified, prospective analysis of a composite safety endpoint including death, myocardial infarction, stroke, or serious adverse events of congestive heart failure, unstable angina or arrhythmia (heart rate 1.50, 95% CI: 0.87, 1.81).

Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence in Patients with Cancer Receiving ESAs

OMONTYS is not indicated and is not recommended for reduction of RBC transfusion requirements or for the treatment of anemia in patients with cancer due to cancer therapy showed decreased locoregional control, progression-free survival and/or decreased overall survival. The findings were observed in clinical trials of other ESAs administered to patients with breast cancer receiving chemotherapy, advanced head and neck cancer receiving radiation therapy, lymphoid malignancy, cervical cancer, non-small cell lung cancer, and with various malignancies who were not receiving chemotherapy or radiotherapy.

**Hypertension**

OMONTYS is contraindicated in patients with uncontrolled hypertension.

**Appropriately control hypertension prior to initiation of and during treatment with OMONTYS**

**Lack of Response to OMONTYS**

For lack or loss of hemoglobin response to OMONTYS, initiate a search for causative factors. Examples of causative factors may include:

- Iron deficiency and excess iron stores due to phlebotomy
- Infection
- Inflammation
- Bleeding

**Laboratory Monitoring**

Evaluate transferrin saturation and serum ferritin prior to and during OMONTYS treatment. Administer supplemental iron therapy when serum ferritin is less than 100 mcg/L, or when serum transferrin saturation is less than 20%. The majority of patients with CKD will require supplemental iron during the course
sensitivity and specificity greater than 80 percent. Estimates of accuracy showed significant heterogeneity. For studies using the albumin-to-creatinine ratio, no meta-analysis could be performed. One study reported that a value greater than 2 mg/mmol (according to the DCA 2000 quantitative analyzer) had the highest predictive value for significant proteinuria—sensitivity and specificity were both 94 percent. A study including information on pregnancy outcomes reported 82 percent sensitivity for perinatal death, with specificity of 97 percent. A meta-analysis of results from studies of albumin-to-creatinine ratio was 0.82, with specificity of 0.59. A quick and accurate method is needed to identify significant proteinuria in women with suspected pre-eclampsia. On the basis of available evidence, the estimated protein-to-creatinine ratio in spot urine samples is a promising test for this purpose. More research will be needed to clarify the clinical value of this test, to assess the use of the albumin-to-creatinine ratio, and to evaluate the ability to predict adverse pregnancy outcomes with either test [Morris RK, et al. Diagnostic accuracy of spot urinary protein and albumin to creatinine ratios as predictors of adverse pregnancy outcome in patients with suspected pre-eclampsia: systematic review and meta-analysis. BMJ 2012; 345:e5432].

Cystatin C Plus
Creatinine Improves Estimation of GFR

An equation adding data on cystatin C to serum creatinine improves accuracy in estimating GFR, reports an article in the New England Journal of Medicine.

The Chronic Kidney Disease Epidemiology Collaboration study included data on more than 5352 individuals enrolled in 13 studies. The researchers developed equations for estimating GFR based on cystatin C alone and cystatin C plus standard-ized creatinine. The equations were validated in a set of 1119 participants from five studies who had undergone GFR measurement.

Compared with equations using either creatinine or cystatin C, the estimated GFR provided better performance in estimating GFR. Although bias was similar between the three equations, precision was higher with the combined cystatin C-creatinine equation. The interquartile range of the difference between estimated and measured GFR was 13.4 mL/min/1.73 m² with the combined equation, compared with 15.4 mL/min/1.73 m² with the creatinine equation and 16.4 mL/min/1.73 m² with the cystatin C equation.

The combined equation also offered increased accuracy and improved classification of chronic kidney disease (CKD). Among participants with a creatinine-based estimated GFR of 45–74 mL/min/1.73 m², the net reclassification index for the presence of CKD (60 mL/min/1.73 m²) was 19.4 percent. Among those with an estimated GFR of 45–59 mL/min/1.73 m², the combined equations correctly reclassified 16.9 percent of participants as not having CKD.

The combined equation based on standardized creatinine and cystatin C offers better performance in estimating GFR, and it may also improve the classification of patients with CKD. The researchers write, “The new equations represent an advance over currently available equations across the range of GFR and in relevant subgroups.” [Inker LA, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012; 367:20–29].

of ESA therapy. Following initiation of therapy and after each dose adjustment, monitor hemoglobin every 2 weeks until the hemoglobin is stable and sufficient to minimize the need for RBC transfusion. Therafter, hemoglobin should be monitored at least monthly provided hemoglobin levels remain stable.

ADVERSE REACTIONS

The following serious adverse reactions observed during clinical trials with OMONTYS are discussed in greater detail in other sections of the labeling:

• Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism

[see Warnings and Precautions]

• Hypertension [see Warnings and Precautions]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of OMONTYS cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice.

Patients with Chronic Kidney Disease

Adverse reactions were determined based on pooled data from two active controlled studies of 1066 dialysis patients treated with OMONTYS and 543 patients treated with epoetin, including 938 exposed for at least 6 months and 825 exposed for greater than one year to OMONTYS. The population for OMONTYS was 20 to 93 years of age. 58.5% male, and the percentages of Caucasians, Black (including African Americans), and Asian patients were 37.4%, 3.1%, and 0.9%, respectively. The median weight adjusted dose of OMONTYS was 0.07 mg/kg and 113 U/week/kg of epoetin.

Table 3 summarizes the most frequent adverse reactions (≥10%) in dialysis patients treated with OMONTYS.

Table 3 Adverse Reactions Occurring in ≥10% of Dialysis Patients treated with OMONTYS

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Dialysis Patients Treated with OMONTYS (N = 1066)</th>
<th>Dialysis Patients Treated with Epoetin (N = 542)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18.4%</td>
<td>15.9%</td>
</tr>
<tr>
<td>Nausea</td>
<td>17.7%</td>
<td>19.6%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15.3%</td>
<td>13.3%</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>18.4%</td>
<td>19.4%</td>
</tr>
<tr>
<td>Cough</td>
<td>15.9%</td>
<td>16.0%</td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteriovenous Fistula Site Complication</td>
<td>16.1%</td>
<td>16.0%</td>
</tr>
<tr>
<td>Procedural Hypotension</td>
<td>10.9%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>15.4%</td>
<td>15.9%</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>15.3%</td>
<td>17.2%</td>
</tr>
<tr>
<td>Pain in Extremity</td>
<td>10.9%</td>
<td>12.7%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>10.9%</td>
<td>11.3%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10.7%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>14.2%</td>
<td>14.8%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>13.2%</td>
<td>11.4%</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>12.2%</td>
<td>14.0%</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>11.4%</td>
<td>11.8%</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>11.0%</td>
<td>12.4%</td>
</tr>
</tbody>
</table>

Seizures have occurred in patients participating in OMONTYS clinical studies. During the first several months following initiation of OMONTYS, blood pressure and the presence of neurologic symptoms should be monitored closely. Advise patients to contact their healthcare practitioner for new-onset seizures, premonitory symptoms, or change in seizure frequency.

Allergic reactions have been reported in patients treated with OMONTYS. Discontinue OMONTYS and administer appropriate therapy if a serious allergic, anaphylactic or infusion-related reaction occurs.

Immunogenicity

Of the 237 patients tested, 29 (1.2%) had detectable levels of peginesatide-specific binding antibodies. There was a higher incidence of peginesatide-specific binding antibodies in patients dosed subcutaneously (1.9%) as compared to those dosed intravenously (0.7%). Peginesatide neutralizing antibodies were detected in vitro using a cell-based functional assay in 21% of these patients (0.8%). In approximately half of all antibody-positive patients, the presence of antibodies was associated with declining hemoglobin levels, the requirement for increased doses of OMONTYS to maintain hemoglobin levels, and/or transfusion of amnium of KDO. No cases of pure red cell aplasia (PRCA) developed in patients receiving OMONTYS during clinical trials.

DRUG INTERACTIONS

No formal drug/drug interaction studies have been performed. Peginesatide does not bind to serum albumin or lipoproteins as demonstrated in vi tro protein binding studies in rat, monkey and human sera. In vi tro studies conducted with human hepatocytes or micromes have shown no potential for peginesatide to induce or inhibit CYP450 enzymes.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Peginesatide was teratogenic and caused embryofetal lethality when administered to pregnant animals at doses and/or exposures that resulted in polyvinyl in OMONTYS- treated pregnant animals only if the potential benefit justifies the potential risk to the fetus.

Administration of peginesatide by intravenous injection to rats and rabbits during organogenesis was associated with embryofetal toxicity and malformations. Dosing was every third day in rats for a total of 5 doses and every fifth day in rabbits for a total of 3 doses (0.01 to 50 mg/kg/dose). In rats and rabbits, adverse embryofetal effects included reduced fetal weight, increased resorption, embryofetal lethality, cleft palate (rats only), sternum anomalies, unossification of sternebrae and metatarsals, and reduced ossification of some bones. Embryofetal toxicity was evident in rats at peginesatide doses of ≥1 mg/kg and the malformations (cleft palate and sternebrae anomalies) and in rabbits (5% - 50%) than the dose of 0.35 mg/kg in patients. In a separate embryofetal developmental study in rats, reduced fetal weight and reduced ossification in rabbits were observed at doses ≥0.5 mg/kg/dose of peginesatide. In a separate embryofetal developmental study in rabbits, adverse findings were observed at doses lower and included increased incidence of fused sternebrae at 0.25 mg/kg. The effects in rabbits were observed at doses lower (5% - 50%) than the dose of 0.35 mg/kg in patients.

Nursing Mothers

It is not known whether peginesatide is excreted in human milk. Because many drugs are excreted into human milk, caution should be exercised when OMONTYS is administered to a nursing woman.

Pediatric Use

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

Gastrointestinal Disorders

Diarrhea 18.4% 15.9%

Nausea 17.7% 19.6%

Vomiting 15.3% 13.3%

Respiratory, Thoracic and Mediastinal Disorders

Dyspnea 18.4% 19.4%

Cough 15.9% 16.0%

Injury, Poisoning and Procedural Complications

Arteriovenous Fistula Site Complication 16.1% 16.0%

Procedural Hypotension 10.9% 12.5%

Nervous System Disorders

Headache 15.4% 15.9%

Musculoskeletal and Connective Tissue Disorders

Muscle Spasms 15.3% 17.2%

Pain in Extremity 10.9% 12.7%

Back Pain 10.9% 11.3%

Arthralgia 10.7% 9.8%

Vascular Disorders

Hypertension 14.2% 14.8%

Hypotension 13.2% 11.4%

General Disorders and Administration Site Conditions

Pyrexia 12.2% 14.0%

Metabolism and Nutrition Disorders

Hyperkalemia 11.4% 11.8%
The Transition from Adolescent to Adult Care

Reduced Kidney Transplant Survival in Adolescence and Young Adulthood: Is it Due to Age, Transfer of Care, or Both?

By Susan Samuel, MD, MSc, and Bethany J. Foster, MD, MSCE

Kidney transplant survival is worse among adolescent transplant recipients compared with older and younger recipients. There are likely complex factors operating at both patient and health care system levels contributing to the increased risk for graft failure in adolescents.

Poor kidney allograft survival was first reported in 1997 by Cecka and colleagues (1). Using the United Network Organ Sharing database, they demonstrated that the 5-year graft survival rate among 13- to 21-year-old kidney transplant recipients was worse than the rates observed in other age groups. Subsequently in 2002, Smith and colleagues (2) showed an increased risk of graft failure in 13- to 17-year-old transplant patients registered in the North American Pediatric Renal Trials and Collaborative Studies database. They also observed that there was a significantly higher number of late acute rejection episodes among those receiving transplants between 6 and 17 years of age compared with younger age groups.

These two studies identified adolescent age at the time of transplant as a determinant of poor graft survival, but did not consider the possibility that it is adolescence itself (a developmental period) that determines graft failure risk. Almost all pediatric transplant patients will eventually enter adolescence—a period of major physical, cognitive, emotional, and social development, and of increasing independence. Adolescence can be a volatile and turbulent time in some patients, which makes this period ripe for complications. It is during this vulnerable developmental stage that almost all adolescents are transferred to adult care—around 18 to 21 years of age in most pediatric institutions across North America. Behavioral changes associated with adolescence and upheaval related to transfer of care may combine to increase the risk of graft failure during this period.

Recently, our group estimated age-specific graft failure rates using the United States Renal Data System (USRDS) database (3), and showed a gradual increase in graft failure rates starting at 11 to 12 years of age, peaking at 19 to 21 years of age, and declining thereafter. Compared with 25 to 29 year-olds with the same time elapsed since transplant, graft failure rates were 20 percent higher among 17 to 24-year-olds, regardless of the age they received the transplant. This study provided strong evidence that graft failure risk is age dependent, and that late adolescence and early young adulthood is a high-risk period. This study did not refute the earlier studies’ conclusions that adolescent age at transplant is a risk factor. Rather, it indicated that individuals transplanted as adolescents enter immediately into a high-risk period. We were unable to account for the effect of transfer of care because transfers are not captured well within USRDS databases.

In 2007, the U.S. Government Accountability Office commissioned a report to investigate whether pediatric transplant recipients are more likely than their adult counterparts to lose access to immunosuppressive medications once Medicare coverage for end-stage renal disease (ESRD) ends 3 years after receiving a transplant (4). They used USRDS databases to study this problem. Although the investigators of the report did not find that graft failure was necessarily associated with loss of Medicare, they found that graft failure risk was higher at 3, 5, and 7 years after transplant for patients who had an 18th birthday during observation period compared to older and younger patients. This high-risk group of patients was defined as ‘transitional’ patients as some of them would have been transferred to adult care during the observation interval. This study also could not ascertain the effect of transfer of care due to the limitations of USRDS data. We could postulate that poor transfer of care may have had a role in determining high graft-failure rates in transitional patients. The association between graft failure and age, therefore, has been clearly characterized in these two studies, but further studies are needed to identify the factors mediating the relationship between age and graft failure and, in particular, the role of transfer of care.

The higher graft-failure risk during adolescence and young adulthood has been postulated to be due to a state of net under-immunosuppression related to some or all of the following factors: puberty-related changes in immune reactivity, de novo exposure to viruses, and under-dosing of immunosuppression medication during a period of rapid growth and nonadherence.

Nonadherence with immunosuppressive medications is probably the most widely cited explanation for poor graft outcomes during adolescence. The prevalence of nonadherence among adolescents can be as high as 43 percent. Several studies have shown a greater degree of nonadherence in adolescents compared with older and younger patients. Failing to take immunosuppressants can be a cause for late acute transplant rejection. Therefore, Smith’s finding of increased late rejection and incomplete rejection reversal in the adolescent age group supports nonadherence as a potential mechanism of graft failure in this age group (2).

There are many reasons for nonadherence. Some have suggested that nonadherence may increase immediately following transfer from pediatric to adult care leading to graft failure. This idea was first put forward over a decade ago by Alan Watson, who observed unanticipated kidney transplant failures in seven of 20 patients in the 3 years following transfer of care. Although studies using large USRDS datasets were unable to account for the effect of transfer of care when examining the relationship between age and graft failure rates, a study of Canadian pediatric transplant recipients found a 2- to 5-fold increased risk in graft failure during the period immediately following transfer from pediatric to adult care (5). Nonadherence after transfer of care could not be quantified in this study.

Poorer graft survival after transfer of care suggests that sudden changes in health care system and provider characteristics may create an environment that exacerbates nonadherence and other behaviors that can accelerate graft failure. Medical care for pediatric patients with ESRD generally tends to be intense and multidisciplinary. Staff-to-patient ratios are high and a large amount of time is usually spent on each clinical encounter. Detailed attention is paid to patient compliance with medical appointments and medication. Although such intense support may not be medically necessary for most adult patients, a sudden change in type of care after transfer to adult-oriented care may be disorienting to pediatric patients, who have been accustomed to receiving intense care and attention all their lives. The shift of focus from family to the individual—with emphasis being placed on the patient’s responsibility for his/her own care—has been identified as a factor which may contribute to impaired adherence to therapy following transfer to adult care.

For individuals with ESRD, adapting to transfer of care may be particularly challenging. On the surface, most adolescent and young adult kidney transplant recipients look like their healthy peers. It is easy to forget that they may have severe cognitive deficits related to childhood exposure to renal failure or other medical problems. It is even easier to forget that even healthy adolescents—while physically fully mature—do not complete frontal lobe develop-
The Transition from Adolescent to Adult Care

There is no research that proves the ideal age from that conferred by transfer of care. Patient and health care system factors may all contribute to age-related graft-failure risk. Perhaps, the most important question is how to improve graft outcomes in this vulnerable age interval. This is most likely to be achieved by providing care that is well matched with the developmental needs of this age group. The first step will be to identify patient-, provider-, and system-level factors associated with better outcomes. Then trials need to test multicomponent interventions at the patient, provider, and system levels to optimize care for this group of patients.

References

Nephrology Transition 101

By Miriam Kaufman, MD, FRCP
P
ediatric nephrology encompasses such a wide variety of conditions and illness severities that it may be hard to imagine that any one transition model could fit for all of nephrology. While it is true that transition programs must be adapted for different populations, there are basics that apply to them all. These include starting young, ensuring knowledge of one’s condition, promoting self-management, introducing the patient and family to the adult system, facilitating appropriate transfer planning/documentation, and providing young adult care that is developmentally appropriate (this last factor is discussed in another article in this issue).

Starting young

There is no research that proves the ideal age to start transition preparation, but many policy statements and consensus papers strongly suggest starting early without suggesting a specific age. One advantage of bringing up the idea of transition care early is that it gives parents hope that their child will survive into adulthood and that plans are being made—they won’t just be “kicked out” when the time comes. Some young people also get the idea that they won’t have their condition when they grow up, since they only see other children at their clinic appointments; raising the issue of transfer and transfer planning from the time of diagnosis may prevent this thinking. One tool for early transition and self-management is the Ready Set...Good 2 Go nephrology timeline (http://www.sickkids.ca/pdfs/Good2Go_Transition/Interventions-Tools/Readiness-checklist/index.html).

Developmentally appropriate services for young adults

The demographics of adult hospitals are clearly skewed towards the geriatric age range. Clinic staff who recognize that young people are still finishing their brain development—and whose executive functions are therefore not fully mature—will be able to approach the young person in a way that recognizes that they are no longer children but have needs that are different from adults. This does not mean that young people must be “babyed” but rather that they will still need help in developing the skills that they need to be self-managing, self-advocating members of their health care team.

When does transition end?

The many life transitions that happen at the end of childhood have different end points (graduation from high school or postsecondary education, finding a life partner, getting a job with good benefits, and becoming autonomous in medical management) and are also met at different ages, sometimes with backward steps along the way. Many adult providers talk about the clinic visit where the “light bulb went on” for a young person in their mid-20s. This could be considered to be the moment when the health care transition ends. Many times there won’t be such a clear-cut event, but rather a gradual move towards maturity and responsibility. A patient-centered approach should incorporate the changing needs of the now-mature patient and the health care challenges that go with being an adult with a chronic health condition. Dr. Kaufman is affiliated with The Hospital For Sick Children, Toronto, Ontario, Canada.
The Transition from Adolescent to Adult Care

How can we measure or predict transition readiness?

By Emily M. Fredericks, PhD

The number of adolescents and young adults with chronic kidney disease or a renal transplant making the transition from pediatric to adult health care is on the rise. However, the transition process often raises concern among providers, parents, and patients. Providers may have a difficult time “letting go” of their patients, and may worry about the risk of medical complications following the transfer to adult-centered care. Parents and adolescents are often concerned about leaving their familiar pediatric providers, and worry about the care they will receive with new providers in an adult clinic. In addition, parents may express concern about whether their adolescent is able to manage their health independently, as may be expected in adult clinics. Thus, there is a need to develop strategies to assess a pediatric patient’s readiness to move to an adult-centered clinic (1–3).

What is “transition readiness”?

Transition readiness is the ability of an adolescent and his/her family and medical providers to engage in the process of moving from pediatric to adult care. Yet, in order to predict readiness, it is necessary to define a successful transition. An important outcome of the transition process is the actual transfer to a new health care setting, provider, or both. However, the transition process does not end with the handoff in the adult clinic. Rather, the process of moving toward independent self-management will continue beyond the transfer of care. As we attempt to measure and predict transition readiness, it is necessary to consider how the transition process impacts patient satisfaction, quality of life, educational/vocational outcomes, as well as medical stability following the transfer to adult care.

How can I assess transition readiness in my clinic?

Practitioners are encouraged to incorporate assessment of self-management skills, health-related knowledge, adherence, and psychosocial support into standard clinical care as we strive to promote optimal long-term outcomes for our pediatric patients. Ideally, the assessment of transition-related skills would be conducted using well-validated measures in the context of standard clinical care. While there is not an accepted “gold standard” transition tool, there is a growing literature supporting measures that assess areas of self-management and transition readiness (4–7). In addition, the American Society of Transplantation Pediatric Community of Practice Joint Transition Work Group has published a web-based transition resource that is publicly available (http://www.a-st.org/content/ast-pcpp-web-resources-transition-adult-care) with resources that are not transplant-specific allowing for wider use.

How will I know when my pediatric patient is ready to transfer?

In this issue, Miriam Kaufman, MD, FRCPC, describes the basics of transition preparation, which can assist pediatric providers in navigating this process early with patients and their families. There are potential barriers to transferring care, which may occur at the level of the patient, parent/family, and the pediatric/adult provider (3). When assessing a patient’s readiness to transfer care, it is important to address potential challenges, which may include medical instability, regimen nonadherence, poor psychosocial functioning, inadequate insurance coverage, and the lack of an identified adult provider.

It has been recommended that patients should not transfer from pediatric to adult health services unless they have the skills they need to function effectively in the adult health care system. Transfer of care should not be based solely on a pediatric patient’s chronological age. Rather, it is recommended that prior to transferring to adult-centered care, the adolescent should be able to describe their health condition, demonstrate responsibility for their health, and have the ability to manage their daily regimen (1–8). In adult settings, patients are typically expected to independently discuss medical care with the treatment team, schedule and attend appointments, refill prescriptions, and adhere to medications and treatment recommendations. This is often a shift in culture from a pediatric clinic, where parents may shoulder much of the responsibility for health management and communication with the health care team. Thus, before transferring a patient to our adult colleagues, it is recommended that pediatric providers foster the development of self-management skills in their adolescent patients by encouraging them to take an active role in their health.

Summary

Before we can reliably predict transition readiness, further work is needed to define outcomes of a successful transition process. At this time, we know very little about how transition readiness skills predict long-term outcomes in the adult health care system. It is important to partner with adult providers to determine factors that are associated with competence and success in the adult health care system following the transfer from pediatricians. In the meantime, it is recommended that pediatric providers routinely assess adolescent and parent perceptions of transition, health-related knowledge, and self-management skills to evaluate readiness to move from pediatric- to adult-focused health care. The assessment of transition perceptions and self-management skills may identify patients and families who could benefit from more intensive support both before and after the transfer to adult care.

Dr. Fredericks is affiliated with the University of Michigan, Ann Arbor, MI.

References


Chronic Kidney Disease in Early Life: The Impact on Cognition, Education, and Workforce Integration

By Debbie Gipson, MD, MS, and Maria Ferris, MD, PhD

The majority of children affected by chronic kidney disease (CKD) will survive to adulthood (1, 2). Adult survivors of childhood onset end stage renal disease (ESRD) will carry with them a legacy of ESRD and its attendant complications, including effects on cognition, education, and employability.

Children with ESRD are at risk for cerebral atrophy, silent and symptomatic cerebrovascular infarctions, and ischemia. However, the cognitive function of children with CKD may be impaired despite normal results on brain imaging. ESRD has been shown to have a negative impact on IQ, memory, and cognitive functions (2). Furthermore, in the national Chronic Kidney Disease in Children (CKiD) study 30 percent to 40 percent of children with mild to moderate CKD (estimated glomerular filtration rate 40 to 90 ml/min/1.73 m²) scored more than 1 standard deviation below the healthy population normative mean in measures of IQ, academic achievement, attention, memory, and executive function (3). Pilot data have shown that IQ improves by an average of 12 points in children with ESRD after receiving a kidney transplant (4). This finding suggests that some of the cognitive impairments demonstrated in dialysis-dependent children with ESRD may improve with resolution of uremia.

Education is often disrupted in children with ESRD due to medical appointments, procedures, and illnesses. Given the documented challenges to cognitive function and chronic illness, one would expect that 40 percent to 45 percent of children with ESRD would receive special education services. Unfortunately, children with ESRD have the same 15 percent placement rate in special education programs as the general United States population of children (5). Additional research is required to assess the type and value of special education services for children within the CKD/ESRD continuum.

Employment status has been evaluated in adult survivors of childhood-onset ESRD (6). In a Dutch cohort, 67 percent of the patients in the study were employed, which is substantially greater than published employment rates of 25 percent to 50 percent of adults with adult-onset ESRD in several other studies (6–10). Compared with healthy age-matched controls, adult survivors of childhood-onset ESRD were more likely to be unemployed involuntarily (19 percent versus 11 percent) and to be employed in positions requiring a lower level of training or education (6). Another study found that adult survivors of childhood-onset ESRD had a 10 point to 15 point decrement in IQ compared with their healthy age-matched counterparts and tended to have a lower final educational/training level than the general population (11). It is hypothesized that health-related disruptions in typical developmental experiences and in education contribute to these findings.

Although additional investigation is required to bolster our understanding of the factors that contribute to the cognitive and educational challenges experienced by children with CKD, we now have evidence documenting the resilience of adult survivors of childhood-onset ESRD based on their employment rates. Our next step is to identify effective intervention strategies to maximize cognitive development, educational achievement, and prospects for employment opportunities equal to the general population.

Optimizing Adherence in Youth With Kidney Transplants

By Bethany J. Foster, MD, MSCE, and Sandra Amaral, MD, MHS

Adhering to a strict medication regimen is difficult for anyone, but it can be particularly challenging for adolescents and young adults. Adherence is a skill that must be learned, and it requires organization, advanced planning, and good problem-solving skills, tools that adolescents and young adults are still developing. In fact, the part of the brain responsible for planning and for considering the impact of actions taken (or not taken) is not completely developed until one reaches their mid-20s! In addition, adolescence is a time for testing limits, trying new things, and exploring different identities—activities that are not particularly compatible with sticking to a strict medication schedule.

Perhaps, not surprisingly, studies that compared medication adherence in teenagers and young adults with that in younger children and older adults have been unanimous in their conclusions: medication adherence is worse among teens and young adults. Unfortunately, a few missed doses can have significant and irreversible consequences for young kidney transplant recipients. Teens and young adults who miss medications and experience rejection episodes are less likely to achieve complete reversal, leading to loss of kidney function and often complete graft loss. Youth between the ages of 17 and 24 years have the highest risk of renal allograft failure of any age group, regardless of their age at transplant (1). Although poor adherence is not the only factor mediating graft loss among youth, it certainly plays a major role.

But what can we do to try to improve medication adherence among adolescents and young adults with kidney transplants? Think of the African proverb “It takes a village to raise a child.” To meet the challenge of medication adherence in this age group requires a collaborative team effort from health care providers, the patient, and their family (2, 3). A number of risk factors for poor adherence have been identified, including factors related to the medication regimen, the health care team, and social aspects. A multifaceted approach is needed to address these risk factors. As clinicians, anything we can do to simplify a patient’s medication regimen—from fewer pills per dose to fewer doses per day—may help young people become more adherent with their treatments. It is also important to ask about side effects. An open and nonjudgmental attitude on the part of health care providers is crucial to promote trust and may also result in better adherence. Adolescent and young adult patients should be interviewed independently from their parents and asked directly about their adherence practices. Questions should be open ended and acknowledge that taking medications every day is difficult. Social factors associated with adherence may be more difficult for a health care team to address. A clinical care team cannot change a family’s structure or financial situation. However, clinicians can provide resources and help families think ahead to prevent lapses in insurance and the supply of medications. Whenever possible, the consistent involvement of a social worker is recommended.

There is no known sure-fire method of improving medication adherence. Education aimed at improving patients’ understanding of their medications, how they work, and why they need to be taken regularly is certainly believed to be necessary, but education alone is clearly insufficient in promoting adherence. Adherence experts suggest that we must not only provide our patients with knowledge, but teach them the skills they need to be adherent, including organizational and problem-solving skills.

The first step in teaching problem-solving skills related to medication adherence is to explicitly acknowledge the challenges of consistent medication
adherence. This may open the door to a more meaningful conversation about adherence. The second step is to find out what interferes with this particular patient taking her medications on schedule. Some of the most common barriers to adherence cited by parents and patients include forgetfulness and poor planning or scheduling (2, 4). In order to overcome these barriers, parents and patients must work together at home to establish routines and clarify roles and responsibilities in managing the medical regimen. The clinician may help families to find solutions to adherence barriers. Simple solutions work best and may include things like setting cellphone reminders or using a pill box. The key is to help the patient to find their own solutions, rather than to “prescribe” solutions for them. Although this approach is certainly more time consuming, it is much more likely to be effective. When possible, having the patient and caregiver meet with a psychologist can be very helpful. Both the patient and the caregiver need to be reminded that adherence is a process and that difficulties with adherence are not always solved on the first attempt.

Clinicians can encourage ongoing parental support, and may guide the gradual transition of responsibility for medication-related tasks from parent to adolescent. It is helpful to establish realistic expectations and assess how much a patient can really do on their own. The process is not easy, and may involve a certain amount of trial and error. To help parents understand the process, clinicians can make parallels between other life skills that a child will gain in adolescence, like doing chores or learning to drive. These tasks also are learned skills, which take time and effort and are most successfully accomplished with gradually decreasing supervision and support from parents.

Adherence should be discussed explicitly at every visit. Just as we would follow up a rash or the effects of a new medication, clinicians should follow up the results of a plan made with the patient to increase adherence. We must find out what worked and what didn’t, and celebrate small successes. As adolescents develop and face new challenges, we must also try to anticipate new adherence challenges. Changes in routine, such as summer breaks or starting college, can pose disruption and can usually be anticipated and discussed in advance.

Support from family and friends is one of the most important factors promoting adherence. Some patients for whom family support is unavailable may benefit from the involvement of a close friend. Clinic visits should be inclusive to significant others or friends, and patients should be encouraged to bring support with them if they choose to do so. Some families find support in the waiting room. Providing opportunities for caregivers to meet each other and patients to interact can be very valuable by providing opportunities to share experiences and find positive role models.

The best approaches to promote medication adherence in adolescents and young adults are inclusive to the family, patient, and health care team but are individualized, and focused on the patient. Remember to empower the patient to identify their own stumbling blocks and pinpoint ways to overcome them. And, above all, remember that adherence may wax and wane; providers must be attentive and provide consistent support throughout.

Dr. Amaral is affiliated with the University of Pennsylvania and The Children’s Hospital of Philadelphia, Philadelphia, PA. Dr. Foster is affiliated with McGill University, Montreal, Quebec, Canada.

References
By Vinay Nair, DO, and Rachel Annunziato, PhD

What is transition?” asked my colleague when I mentioned the topic of this article. As I began to explain the science and philosophy of the transition from pediatric to adult care my coworker’s expression became more thoughtful, although it was obvious that he didn’t know much about the topic. Later it became clear that there is a large amount of variability in different individuals’ knowledge of transition and in the effects of a rocky transition on those being transferred. This inconsistency exists despite the fact that almost all of my colleagues have had at least one bad experience in caring for such patients. Unfortunately, this scenario is more common than many practitioners would like to admit. But what’s the big deal? If there’s a problem, it’s with the patient and their family and not because they transitioned to an adult practice, right?

Unfortunately, that answer is probably wrong. Transition of care is an important concept for all patients but especially for those with life-altering chronic medical conditions, such as patients with CKD or kidney transplants. The mortality rate for patients between the ages of 18 to 24 years is twice as high as that for those aged 12 to 17 years (1). Renal transplant recipients in this age group also face a higher risk for rejection and graft failure due to chronic rejection (2). A landmark study of kidney transplant recipients by Watson (3) was one of the first to demonstrate that poor outcomes in this age group can be associated with the transfer out of a pediatric nephrology practice. It has been suggested that young patients are unhappy with their care after the transition, and as Watson speculated, nonadherence may be a manifestation (3). Other qualitative and mixed-methods studies have illuminated specific concerns that patients have about transitioning to an adult practice (4). For instance, a common perspective is that adult clinicians will not be as patient or understanding as their pediatric counterparts (5). Unfortunately, the volume of literature demonstrating problems with the transfer process far outweighs that evaluating potential solutions. In order to improve this process, pediatric and adult personnel must collaborate to understand the barriers to a successful transition. And although transition is often discussed among pediatric and adolescent practitioners, the adult voice is lacking (6).

Adult physician perspectives

From an adult practitioners’ perspective, there is often inadequate communication from the referring pediatricians. For example, Okumura (7) reported that only 62 percent of internists found it easy to discuss a patient’s transfer with a pediatric provider. In addition, adult nephrology practices generally have a larger patient volume with only a small minority of young adults, because while all pediatric patients transition to adult care very few adult patients come from a pediatric practice. It is therefore difficult to change practice styles based on this minority. But perhaps most importantly, patients may not be ready to take responsibility for their own health care, and therefore they may not perform well in an adult practice. Expectations may be unrealistic and patients unfamiliar with their medical history. Many young patients have had relationships with their pediatricians for years, and now, transplant recipients starting several years before the transfer (10). In addition to offering information on health care management, a “Transition Checklist” is completed by patients and their families before the transfer, the results of which are distributed to the adult practice (10). This helps families take the lead in sharing information with their new providers, and pediatric team members can highlight key areas such as patient apprehension about transfer, previous history of nonadherence, and other issues. The pediatric team identifies deficits in skills that are critical for assuming primary responsibility for one’s health care (e.g., ordering refills of medications or scheduling appointments), and any gaps that remain before the transfer are addressed before the adult patient is fully cared for (8). If these practices are not fully completed, adult teams can conduct their own brief assessments after transfer. In addition, many Internet-based tools are readily available to assess transition readiness and identify pertinent literature. A “medical passport”—a brief synopsis of the patient’s medical history they carry with them—is another simple yet useful method of communication with the adult team (11).

Finally, innovative methods to improve communication with patients during transition may also benefit both pediatric and adult practices. A common theme among studies revealing poor post-transfer outcomes is that patients get lost or disengaged during the transition process (10). An Australian group working with pediatric endocrinology patients investigated whether corresponding with patients via a variety of communication modes (e.g., text messaging or social networking) improved compliance with appointments after the transfer (11). Their results suggest that such modalities may also be useful in patients with kidney disease.

Finally, although many guidelines exist for pediatric practices few have been developed for adult settings (9, 11, 13). Similarly, there is a lack of Internet-based tools aimed at the adult clinic. Transition may seem to end after transfer to an adult practice, yet practicing adult providers know this isn’t true. Acknowledging that transition continues after transfer, improving resources for adult practitioners needs to become a priority. Publishing papers on transition topics in popular high-impact general medical journals could help promote awareness to internists and specialists alike. Lastly, physicians are more comfortable using tools learnt during training, but transition is not usually taught in medical school, residency, or fellowship. Typically, learning about transition arises from the need in practice. Encountering young adults who are transitioning during one’s medical training would better equip physicians to care for such patients in the future.

It is reasonable to say that adult and pediatric providers can do better to assist patients with kidney disease as they transition to adult care. Improving the transition process hinges on communication, collaboration, and education. Good communication between pediatric and adult providers is critical when transitioning patients. Both pediatric and adult practitioners need to work together to develop and test programmatic solutions that target deficits in care. And perhaps it’s time to begin transition training earlier in the career of our future nephrologists. Simply stated, young adults should have the best outcomes, not the worst. We owe it to young adults to educate ourselves, and at times to change our practice style, to better serve this vulnerable population.

References

Pediatric kidney transplant recipients usually transition their care to the adult transplant nephrology team upon reaching the age of majority (between the ages of 18 to 21 years) (1). During the transition, the young patients often lose their health insurance coverage and this is one of the major reasons for nonadherence and allograft loss in this population. For many years, health care coverage for young adults has been known to be insufficient, but these deficits become especially dire for the transplant recipient. In fact, young adults are the highest uninsured patient group in the United States (2); two of five young adults (ages 19 to 25 years) report they are uninsured in 2011 (3). Limited insurability is one of the greatest barriers to successful outcomes in solid organ transplantation and especially afflicts the young adult transplant recipient.

The reason young adult transplant recipients or patients transitioning a gap in their health care coverage is that insurance eligibility criteria change as a child ages. Aging-out of childhood health insurance poses risks for disruption in access to care, with impaited coverage for in- and outpatient care and post-transplant immunosuppressive medication. It is essential that the transition team be able to predict and prepare for changes in insurance eligibility in order to optimize the patient’s opportunity to continue post-transplant care and avoid lapses in the ability to pay for immunosuppressive medications, which alone can cost the uninsured patient between $10,000 and $14,000 per year (4).

Preparing for a patient’s age-out of coverage is a daunting task due to complex state, federal, and private insurance rules (5). Although many of these have changed with the passage of the Affordable Care Act (ACA)—and clear recommendations for benefits have been made by the Committee on Child Health Financing for children from birth to age 26 (6)—the systems are still complex and fraught with state-to-state variability.

Transplant recipients are usually insured through a combination of Medicare, Medicaid, and/or private insurance policies (Figure 1). Medicare Part A covers hospital insurance, with capitated and co-pays for the inpatient stay. Part B of Medicare pays for physician visits and outpatient expenses. There are monthly premiums for Part B coverage and the outpatient physician charges and laboratory work are paid at 80 percent; thus, the patient is still responsible for 20 percent of the charges in addition to the monthly premium. Often a patient needs supplemental insurance for the uncovered 20 percent. Medicare part B also covers immunosuppressive medication charges at 80 percent up to 36 months after the transplant. However, if the patient’s disability is not due to ESFD and they had Medicare coverage at the time of transplant there is no time limit on coverage for antirejection medications. Medicare pays only for antirejection medications, therefore it is important to be aware that the costs of other medications often used in conjunction with the antirejection regimen will not be covered. Yet when children reach adulthood they are no longer eligible for indicators for ongoing social security disability benefits. Therefore, at the same time that young adult patients transition from the pediatric to the adult clinic they often lose their Medicare coverage.

Access to care can be particularly challenging for the young adult transplant recipient. Many of these young adults have resided in the United States for most of their lives as children of undocumented parents. This population of patients does not qualify for patient assistance programs, county medical services, or Medicaid because these programs require legal resident status. Some states have Medicaid programs that provide for immunosuppressive medication coverage, usually for 2 to 3 years, without proof of legal residency; however, caring for these patients often requires altruistic efforts from the medical team.

The challenges for transplant teams participating in the patient’s transition from the pediatric to adult clinic is to plan ahead for potential gaps in insurance and ensure a reliable source of immunosuppressive medications. This must be done months before the patient reaches an age where their insurability is at risk. Often the efforts required to ensure that a young patient will be able to pay for their post-transplant care means an aggressive search for patient assistance programs, insurance exceptions, health care providers willing to volunteer their time to care for the undocumented, and creative strategies in order to ensure that the “gift of life” is not squandered due to limits on insurability. Meeting this challenge requires an enormous time commitment by the transplant team, and often a dedicated financial support team, to sort through a complex morass of state, federal, and private insurer rules and regulations. Many providers will find that the time required to help this most vulnerable group of transplant recipients is not reimbursable. Ultimately, the success of the young adult with a kidney transplant relies on rigorous preparations made by the pediatric transplant team that allow successful transfer of the patient to the adult setting. Additionally, health care providers must be active in public policy discussions to promote optimal insurability for this vulnerable patient population.

References
Young Adult Clinics—Turning a Dream Into Reality

By Paul Harden, MB, ChB, FRCP

Managing young adult patients aged 16 to 25 years with end stage renal disease (ESRD) is a challenge for the whole multidisciplinary health care team. Approximately 50 percent of this age group in any adult kidney unit will have transitioned from pediatric nephrology practice (see the article by Kaufman in this special section), while the remainder will present initially to adult services. The proportion presenting through pediatric care will vary according to local practice, as transfer to adult care can occur at different ages ranging from 16 to 25 years. The combined young adult ESRD population will make up approximately 2.5 percent of the total ESRD population in any one unit, and there is a real danger that such a small subset will be lost in the sea of much older dialysis and transplant patients. Frequently, individual young adult patients will be geographically and socially isolated from peers on dialysis or with functioning kidney transplants.

Adolescent and young adult patients are at a critical point in their educational, social, physical, and psychological development that will shape their future life. The presence of ESRD can greatly impede success in education, relationships, and independent living, which can result in a damaging reduction in self-esteem and clinical depression. Young adulthood is a time of increasing independence and tremendous peer pressure to conform to the “model” young adult, which may lead to a lack of commitment to their chronic illness manifesting as nonadherence with medical appointments, medication regimens, and dialysis attendance. This may result in a 2- to 3-fold increased risk of premature transplant failure with the potential difficulty of future transplantation due to sensitization. Dialysis nonadherence may lead to recurrent hospitalizations due to uncontrolled fluid overload, hyperkalemia, and increased mortality.

Young adult patients share little in common with most of the older patients within any kidney provider service and frequently, the multidisciplinary staff managing their care have difficulty engaging with this population. Feedback from questionnaires and focus groups young adult patients would prefer to attend outpatient clinics with young peers, have continuity of care with key health care professionals with whom they can relate, and have flexibility of health care delivery. An effective approach is to establish a young adult clinic for all 16- to 30-year-old patients with ESRD, providing an opportunity for peer interaction and support in addition to the traditional health care team. It may prove difficult to encourage young adults to interact with one another in the traditional hospital outpatient setting, as many individuals will leave their individual medical consultations are completed. One approach to overcome this barrier is to consider scheduling the young adult clinic in a more youth-friendly environment within a community center, such as a sports club or college facility, rather than the traditional hospital outpatient facility. In this setting it will be possible to establish a young adult patient youth-club environment which will help catalyze peer interaction. Initially this may prove difficult in any adult renal unit as there will be a small number of patients who may have limited interests in common beyond their renal failure and associated treatment. Peer interaction can be catalyzed by the involvement of a youth worker or other key team member who could engender a youth club environment and ensure collective participation. In the optimal setting, team activities—such as a pool competition, bowling, or traditional board games—can break down any social barriers and encourage peer interaction amongst the patient group. This rapidly leads to comparative discussion of their experiences of kidney disease from both positive and negative perspectives. Once introduced, the peer interaction will spread beyond the young adult clinic environment through social networking vehicles such as Facebook or simple text messaging.

A key to the success of a young adult clinic is a youth worker or equivalent key team member. Most hospital teams will not be very familiar with the role of youth workers who tend to work in community settings with young people aged 12 to 25 years. Their roles have been predominantly developed supporting young adults with drug-dependence problems, HIV disease, and physical disabilities. The unique and key roles of youth workers include building self-esteem, providing individual support to young adult patients, and helping with social and personal development, since young adults with ESRD frequently have delayed development of social skills due to the isolating nature of their illness. It is important to identify a small team of key multidisciplinary health care staff who will run the young adult service. This team should ideally comprise a key physician(s), nurse practitioner(s), and youth worker. Limitation in the number of key individuals will facilitate continuity of care and more readily instill trust amongst the young adult patients. It is essential to have a close and integrated link with the local pediatric nephrology team to insure seamless integrated transition of young adult patients transferring from pediatric to adult care. Ideally the young adult service will have customized access to psychological, dietetic, pharmacologic, and social worker support. It is important to recognize that the needs of young adult patients differ from the typical older ESRD patient as they are embarking into the adult world and often require support to optimize educational, employment, and social development.

Adolescent nephrology units should develop a strategy for a comprehensive young adult service which should have a young adult clinic as a core component. In addition, other useful components would include community outreach by the youth worker who can visit individual young adult patients on a one-on-one basis in the community to provide targeted individual support. This will frequently involve helping to build confidence and self-esteem but may involve provision of support in other ways, such as helping to a small number of young adult patients into a sea of old patients stifling any peer interaction and leading to peer isolation. Young adults with ESRD have a long future ahead of them and we should ensure we provide additional targeted support to allow them the opportunity to maximize their future potential and minimize the tragic risk of increased morbidity and mortality from nonadherence and a lack of engagement with their chronic illness and health care.

References

New Method May Lead to Better CKD Testing

Researchers at Translational Genomics Research Institute (TGen) of Phoenix, AZ, have developed a promising way to isolate exosomes—tiny cell components that contain genetic and other useful information—from urine.

Exosomes are being widely studied because they may contain biomarker clues that could serve as the basis of new early diagnostic tests for chronic kidney disease (CKD). Found in urine, these cellular components may provide information about the very earliest changes in kidney function.

“Our method of extracting exosomes from urine is simple, fast, and easily adapted to clinical research, so we can ultimately help physicians provide better therapies for their patients,” said Johanna DiStefano, PhD, director of TGen’s Diabetes, Cardiovascular and Metabolic Diseases Division, and senior author of a report on the research that appeared in the July issue of Kidney International.

The plasma membrane in mammalian cells can fold into tiny containers called endosomes. Sometimes the membranes of some of the endosomes can in turn be internalized into even smaller vesicles, called multivesicular bodies. These become exosomes when the multivesicular bodies again merge, become part of the cell membrane, and break open to release their contents outside of the cell.

Exosome evaluations in urine samples would be useful in comparison to conventional kidney tissue biopsies, the group noted. “Unlike a kidney biopsy—an invasive and expensive procedure that provides only a small sample from one of two kidneys—urinary exosomes provide a full representation of the entire urinary system,” said Lucrecia Alvarez, PhD, the study’s lead author.

MicroRNAs (miRNAs) are important regulators of gene expression and have been linked with renal development and disease. Last year, other researchers found that in patients with severe, chronic renal failure, circulating levels of total and specific miRNAs were reduced in comparison with mild renal impairment or normal renal function. A report in Nephrology Dialysis Transplantation found a strong correlation exists between detected circulating miRNAs and eGFR.

In the current study, TGen researchers looked at six different methods, and found the best method for isolating exosomes was a modified protocol of an available exosome precipitation reagent called ExoQuick-TC. That reagent alone didn’t yield high quantities or pure preparations of cell proteins and RNA, which would harbor biological clues. The TGen modification of the protocol led to the highest yields of miRNA and mRNA, which can subsequently be used in genetic profiling experiments, the study showed.

Currently, CKD is typically diagnosed by detecting increased levels of urinary albumin (a protein that is filtered out of urine in healthy kidneys) or of serum creatinine (a breakdown product of creatine, which is part of muscle).

The new TGen method has “strong potential for identifying and characterizing exosomal biomarkers from urine,” with implications for diagnosis and treatment of chronic kidney disorders, Alvarez said. 

Amgen Acquires KAI Pharmaceuticals

Amgen Inc. recently completed its acquisition of KAI Pharmaceuticals for $315 million. Initially agreed to on April 10, Amgen said the move was spurred by the “compelling” phase 2A trial results of KAI-4169, KAI’s compound to treat hyperthyroidism. The deal calls for Amgen to make a loan to KAI so it can plan late-stage trials of the drug.

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Indication:

myfortic® (mycophenolic acid) delayed-release tablet is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine and corticosteroids.

Important Safety Information:

WARNING: EMBRYOFETAL TOXICITY, MALIGNANCIES, AND SERIOUS INFECTIONS

• Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Females of reproductive potential (FRP) must be counseled regarding pregnancy prevention and planning.

• Immunosuppression may lead to increased susceptibility to infection and possible development of lymphoma and other neoplasms. Only physicians experienced in immunosuppressive therapy and management of organ transplant recipients should prescribe myfortic® (mycophenolic acid) delayed-release tablet. Patients receiving myfortic should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

• myfortic® is contraindicated in patients with hypersensitivity to mycophenolate sodium, mycophenolic acid (MPA), mycophenolate molestil (MMF), or to any of its excipients.

• Embryofetal Safety: myfortic can cause fetal harm when administered to a pregnant female. Use of myfortic during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations.

Please see additional Important Safety Information and Brief Summary of Prescribing Information, including boxed WARNINGS, on adjacent pages.
with chronic kidney disease who are on dialysis. The parathyroid glands release a hormone that helps control the amount of calcium in blood. When the glands fail to function properly the amounts of calcium and phosphorous may rise to dangerously high levels. Amland said patients with kidney disease often develop parathyroidism; this condition can worsen as kidney function declines, Bloomberg Businessweek noted in coverage of the acquisition.

Based in Thousand Oaks, CA, Amland had total product sales in 2011 of $15.3 billion, and research and development expenses totaling $3.2 billion. In March, Omnonsyn (peginesatide, manufactured by Affymax) was approved for increasing red-blood-cell counts in patients on dialysis, the same therapeutic area of Amgen’s biggest kidney-related drugs. The New York Times reported at the time that Amgen had garnered $40 billion in revenues for its family of drugs over the past 23 years. Amland recently reported it is expanding its portfolio of drugs for patients with kidney disease and those with many other conditions.

Until recently, the South San Francisco, CA–based KAI Pharmaceuticals was a drug discovery and development company with multiple, novel clinical-stage programs in the areas of kidney disease, cardiovascular disease, and pain management, according to the technology listing directory website Crunchbase.

BioWorld reported that KAI-4169 has the same mechanism as Amgen’s oral calcimimetic, parathyroid-hormone–lowering drug Sensipar (cinacalcet), but with patent protection extending into the late 2020s. KAI-4169 is able to lower the hormone to the same extent as Sensipar, but “KAI-4160 does not have the adverse gastrointestinal events seen in 20 to 30 percent of patients taking Sensipar,” BioWorld noted.

Ferumoxytol is Approved in Europe

The injectable iron drug Feraheme (ferumoxytol) received European approval to treat iron deficiency anemia in adult patients with chronic kidney disease on dialysis. This translated into a $15 million milestone payment from Takeda Pharmaceutical company to its partner AMAG Pharmaceuticals, the manufacturer of Feraheme.

The drug is now being tested as a treatment for anyone with iron deficiency anemia. In July AMAG completed a second phase III trial in 880 patients at 136 sites worldwide that confirmed earlier findings that the drug increased hemoglobin levels in general patients with iron-deficiency anemia.

“With both phase III studies in our global registrational program for Feraheme now complete, we will seek approval for Feraheme for the treatment of a broader population of patients,” said Lee Allen, AMAG’s chief medical officer. The company plans to submit a marketing application for approval of Feraheme in the United States for the expanded indication by the end of this year. Takeda Pharmaceutical plans to file for approval in Europe next year, AMAG reported.

AMAG has sharpened its business focus lately and reorganized in the past few months. The company aims “to focus resources on Feraheme and on expanding its product portfolio with specialty drugs.” AMAG also reported it will stop production of GastroMark, a contrast agent used in bowel magnetic resonance imaging, and has decided to simplify its cost structure and plans to divest its manufacturing facility, with a loss of 45 jobs. The Wall Street Journal reported on July 18 that the cut is about one-fourth of AMAG’s work force.

According to the July 26 AMAG announcement, the company’s total product revenues in the United States for the second quarter of calendar-year 2012 were $14.1 million, a 10 percent increase from $12.8 million reported in the same quarter of 2011. AMAG confirmed expectations of growth and noted in its half-year report that 2012 revenues at this point are on track for Feraheme product revenues of $55 million to $58 million, excluding any royalties and product sales outside the United States. The company also expects to hit milestone payments totaling $33 million from regulatory approvals and commercial launches.

Please see Brief Summary of Prescribing Information, including Boxed WARNINGS, on adjacent pages.
Trial Questions Safety and Efficacy of Phosphate Binders in CKD

The longest placebo-controlled trial of phosphate binders conducted to date challenges the drugs’ utility in patients with chronic kidney disease (CKD) and points to the drugs’ potential harm to patients’ cardiovascular health. The findings, which were published recently in the Journal of the American Society of Nephrology, indicate that additional studies of the safety and efficacy of phosphate binders are needed.

**Surprising trial results**

Given the association between higher levels of phosphorus and mortality in patients with CKD, phosphate binders are commonly prescribed to patients with the disease even though they are approved only for patients with kidney failure.

“In the last several years there have been no less than a dozen observational reports demonstrating that higher serum phosphorus values within the normal range are associated with cardiovascular events, progression of CKD, and mortality,” said Geoffrey Block, MD, of Denver Nephrology, who is the lead author of the study. “This has been shown in patients with or without kidney disease but of course, patients with kidney disease are much more prone to having serum phosphorus at the high end of normal given the reduction in renal excretion of phosphorus.”

To determine the effects of phosphate binders on parameters of mineral metabolism and vascular calcification among patients with CKD, Block and his colleagues evaluated the effects of different phosphate binders in patients with moderate to advanced CKD and normal or near-normal serum phosphorus levels. The investigators randomly assigned 148 patients with estimated GFRs of ≥ 20 to 45 mL/min/1.73 m² to receive calcium acetate, lanthanum carbonate, sevelamer carbonate, or placebo. The primary endpoint was a change in mean serum phosphorus level from baseline to the average of months 3, 6, and 9.

“The results of the trial were quite surprising,” said Block. “Despite using substantial doses of all three medications and achieving the expected reduction in urinary phosphate excretion, serum phosphorus levels were reduced very modestly.” Specifically, serum phosphorus decreased from a baseline mean level of 4.2 mg/dL in both active and placebo arms to 3.9 mg/dL with active therapy and 4.1 mg/dL with placebo. Phosphate binders, but not placebo, decreased the mean level of 24-hour urine phosphorus by 22 percent. The median level of serum intact parathyroid hormone remained stable with active therapy and increased with placebo.

Active therapy did not significantly affect plasma levels of C-terminal fibroblast growth factor 23, which has been associated

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**Myfortic**

(mycophenolic acid) delayed-release tablets

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**INDICATIONS AND USAGE**

Myfortic (mycophenolic acid) delayed-release tablets are indicated for the prophylaxis of organ rejection in patients receiving antithymocyte globulin or antithymocyte globulin in combination with cyclosporine and corticosteroids.

CONTRAINDICATIONS

Mycophenolic acid (MPA) is contraindicated in patients with a hypersensitivity to MPA, mycophenolic acid, mycophenolate mofetil, or any of its excipients.

**WARNINGS** (SEE BOXED WARNING)

EMOTIONAL TOXICITY

Myfortic can cause fatal harm when administered to a pregnant female. Use of Myfortic during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including heart, lung, and eye anomalies (see WARNINGS). Myfortic use is not recommended during pregnancy. For recommended pregnancy testing and contraception methods, see PRECAUTIONS: Pregnancy Exposure Prevention and Planning. Pregnancy and Other Reproductive Functions

Patients receiving immunosuppressive regimens including combinations of drugs, including Myfortic, may present a greater risk for lymphoproliferative disease or lymphoma. In a retrospective analysis of patients treated with Myfortic, the risk of developing lymphomas and other malignancies, particularly of the skin (see ADVERSE REACTIONS), was increased. The risk appears to be related to the intensity and duration of immunosuppression rather than the use of any specific agent. Use of Myfortic for lymphoproliferative diseases in Myfortic-treated patients were comparable to the mycophenolate mofetil group in the phase II and maintenance study (see ADVERSE REACTIONS). An increased risk of lymphoproliferative disease or lymphoma in patients receiving Myfortic therapy has been reported; however, it is unknown whether this increased risk is due to Myfortic alone or concomitant use of other drugs. Therefore, it is important for patients to receive ongoing surveillance for signs and symptoms of lymphoproliferative disease or lymphoma. In addition, the presence of lymphoproliferative disease or lymphoma in patients receiving Myfortic should be reported to the investigator. Only physicians experienced in immunosuppression therapy and staffed with adequate laboratory and supportive medical resources. The physician should be aware that patients treated with mycophenolic acid may present with lymphoma and other neoplasms. Only physicians experienced in immunosuppression therapy should be responsible for maintaining patient safety and should have complete information available for the treatment of the patient (see WARNINGS and PRECAUTIONS).

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- Mycophenolic acid is contraindicated in patients with a hypersensitivity to Mycophenolic acid.

**Marketing Experience**

Consider PML in the differential diagnosis in patients reporting neurological symptoms and conditions, including Polyomavirus infections. Polyomavirus infections in transplant patients may be associated with an increased incidence of digestive system adverse events, including infrequent bowel movements, abdominal pain, and/or diarrhea.

**Drug Interactions: Oral Contraceptives**

- Mycophenolate mofetil (MMF) co-administered with oral contraceptives, (e.g. birth control pill, transdermal patch, vaginal ring, injection, and implant) with caution and additional barrier contraceptive methods should be used.

**Pregnancy Exposure Prevention and Planning**

- Mycophenolate mofetil (MMF) is a hormone that regulates phosphate excretion in the body. The potential mechanism for the increase in bone turnover activity and serum alkaline phosphatase levels in patients receiving MMF is likely to be mediated by resulting changes in the intracellular levels of cellular calcium and vitamin D metabolites. The increases of 15.4 percent versus 3.4 percent). 

**Study Design**

1. A randomized, double-blind, placebo-controlled study of patients with CKD stage 4 undergoing renal transplantation. 
2. Patients were assigned to receive once-daily oral therapy with MMF or placebo for 4 days.

**CONCLUSION**

The increase in bone turnover activity and serum alkaline phosphatase levels in patients receiving MMF is likely to be mediated by changes in the intracellular levels of cellular calcium and vitamin D metabolites. The increases of 15.4 percent versus 3.4 percent. 

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1. The nephrology community to continue...

**Study co-authors include**

- David C. Wheeler, MD, Martha S. Persky, Bryan Kestenbaum, MD, Markus Ketteler, MD, David M. Spiegel, MD, Matthew A. Allison, MD, John Asplin, MD, Gerard Smit, PhD, Andrew N. Hoofnagle, MD, PhD, Laura Kooienga, MD, Ravi Thadhani, MD, PhD, Michael Mandell, MD, Myles Wolf, MD, and Glenn M. Chertow, MD.

By Grant Olan

As the clock winds down to the start of Fiscal Year 2013 on October 1, 2012, congressional leaders have reached an agreement to keep the government funded for an additional 6 months. The deal would avoid a last minute shutdown, move the budget and a possible government shutdown before the November election. Congress is expected to pass the continuing resolution this month, which would provide government funding through March 2013 at the levels Congress agreed to when it passed the 2011 Budget Control Act. However, Congress’s hands full with other contentious business this fall. Topping the list—sequestration, which is Washington-speak for automatic across-the-board cuts totaling $1.2 trillion. Part of the Budget Control Act passed in the summer of 2011, these cuts are slated to take effect beginning January 2013. Unless Congress repeals or replaces sequestration with another deficit reduction plan, these cuts will apply to all defense and "non-defense discretionary" programs.

Nondefense discretionary funding supports medical and scientific research, as well as education and job training, infrastructure, public safety and law enforcement, public health, weather monitoring and environmental protection, natural and cultural resources, housing and social services, and international relations. If sequestration takes effect, funding for these core functions of government would be chopped by a whopping 8 percent or more.

ASN is conducting a concentrated effort this fall to prevent these potentially devastating cuts. The society has teamed up with more than 3000 organizations in the nondefense discretionary community to call for a balanced approach to deficit reduction. Stay tuned for more information about ASN’s fall legislative agenda.

Beyond sequestration, Congress will also have to decide what it wants to do about raising the U.S. debt ceiling (the amount the United States is expected to hit by early 2013 for the third time since 2011). Moreover, Congress will tackle how to prevent a 30 percent cut to Medicare physician payments under the flawed Sustainable Growth Rate (SGR) formula from taking effect in January 2013. ASN is very concerned about the impact these cuts will have on physicians and the highly vulnerable population of patients with kidney disease. The society is collaborating with others in the health care community to advocate for a permanent replacement of the SGR and recently sent a letter to the House Ways and Means Committee with suggestions for addressing this issue.

When it comes to promoting the highest quality care for patients, ASN is on the front lines to ensure Congress hears the voices of our members—not just on sequestration and the SGR but on a number of important policy priorities. To learn more, visit ASN’s recently redesigned “Public Policy” website at http://www.asn-online.org/policy_and_public_affairs/.
Kick off

ASN Kidney Week 2012
with Early Programs

The following 1- or 2-day courses (October 30–31) require separate registration from the ASN Annual Meeting (November 1–4).

- Advances in Geriatric Nephrology: The Dimitrios G. Oreopoulos Memorial Program
- Advances in Research Conference: Autoimmunity and Alloimmunity
- CKD: A Recipe for CardioVascular Disaster (CVD)
- Critical Care Nephrology: 2012 Update
- Diagnosis and Management of Disorders of Acid-Base, Fluid, and Electrolyte Balance
- Dialysis Facility Medical Directorship
- Fundamentals of Renal Pathology
- Glomerulonephritis Update: Diagnosis and Therapy 2012
- Interventional Nephrology for the General Nephrologist

- Kidney Transplantation for the General Nephrologist
- Maintenance Dialysis: Principles, Practical Aspects, and Case-Based Workshops
- Maintenance of Certification: NephSAP Review and ABIM Modules
- Onco-Nephrology: What the Nephrologist Needs to Know about Cancer and the Kidney
- Professional Development Seminar
- Renal Relevant Radiology
- Update in Patient-Centered Outcomes Research in Kidney Disease

Register online at www.asn-online.org/KidneyWeek
The Transition from Adolescent to Adult Health Care

This month, ASN Kidney News editorial board member Edgar Lerma, MD, FASN, interviewed Lorraine Bell, MD, FRCPC, of McGill University and the Montreal Children’s Hospital-McGill University Health Centre in Montreal, Quebec, Canada.

Dr. Lorraine Bell

Q: What is “transplant transition” and how did you get involved in this area?
A: To me, “Transplant Transition” is a process of helping young organ transplant recipients progressively prepare themselves for adulthood. It encompasses the years before they transfer to adult health care as well as a period of time afterward.

My interest in transition began over a decade ago. More and more patients I’d known for years were transferring to adult care. Some really struggled, and a small number of them died unexpectedly. I wanted to better understand what was going wrong and how we could improve the situation.

I have also had the fortune to be actively involved in the field of transition with the American Society of Transplantation (AST; http://www.a-s-t.org/). This gave me a wonderful opportunity to organize and chair the International Consensus Conference on Transition for Transplant Recipients. We had more than 60 participants with a diverse range of expertise, and the conference report and recommendations were published in the American Journal of Transplant in 2008. More recently, I’m thrilled to be chairing the AST joint adult-pediatric workgroup on transition. We have some exciting projects underway that build on many of the consensus conference recommendations.

Q: Is transition a concern only for transplant physicians?
A: Definitely not—it’s a continuum and involves all health practitioners who care for patients with a childhood-onset chronic health condition.

Q: When is the ideal time to begin talking about transition? Is there a time frame that one should take into consideration from both the patient and physician perspective?
A: I believe the concept of transition needs to be introduced at a very early stage in the illness. Many families need help preparing their children with chronic health conditions for adulthood and for the challenges and complexities of adult life. It can be so tempting to “overprotect” these children, yet they need to acquire the same educational and social skills as their healthy peers. In addition, they have added responsibility of learning to manage and be responsible for their medical needs.

The actual “transfer-preparation” processes usually start around the age of 11 to 12 years, and continue progressively into early adulthood.

Q: What are the typical challenges of transplant transition?
A: A huge challenge is the timing of transfer—usually it happens during the developmental phase when risk taking peaks and the brain’s executive control mechanisms are not fully established. It may also coincide with other major life events, like getting a first apartment, starting college or work, moving to another city, or involvement in strongly emotional relationships. These can all play havoc with the young person’s adherence to medical treatment.

Other challenges are related to the patients’ preparedness and social maturity. With longstanding chronic illness there can be delays in achievement of social developmental milestones. These youths may not have enough confidence or the skills to advocate for themselves; they may feel lost, bewildered, or even alienated in an adult system of care, where independence is expected and assumed and appointment times are short.

Continuity of health insurance coverage can also be a very big issue.

Q: I suppose that a team approach is the key to a successful transition. Please discuss how important this is, and the roles that each team member plays.
A: A team approach is integral. In the pediatric setting nurses play a pivotal role—usually they provide most of the teaching, preparation, and support for patients and their families throughout the transition process. Social workers help with family difficulties, financial issues, insurance planning, and practicalities, such as transportation, budgeting, and other aspects of independent living. Psychologists contribute in several ways and neuropsychological assessment is one of their key functions. Children with early onset chronic illness may have particular delays or cognitive challenges that require timely intervention to help optimize their educational potential. Psychologists can also help evaluate youth for whom there are concerns about adult decision-making capacity. And, as one would expect, they’re very important in helping with issues of adherence, adaptation, anxiety, depression, and behavior. Adolescent medicine specialists assist with overall preparation, guidance, and support of the process. Some teams also include a nutritionist, pharmacist, and a primary care physician.

Although a team approach is usually the norm in complex pediatric care, it is often an exception in the adult system. Yet cost effectiveness for this approach has been shown in studies of young adult clinics for cystic fibrosis and for diabetes.

Q: Are there any key signs that can help you identify patients who may have some difficulty with transition?
A: There are always surprises, and at times they can be very challenging to predict. For example, the patient one least expects to have a major problem may be the one who ends up in serious difficulty and vice versa. But generally, it seems that adolescents with a good family relationship, effective self-management and self-advocacy skills, and a strong social support system are likely to do best. I worry most about patients who have a lot of rebellious behavior and poor family or peer support. Young people who have dropped out of school are also at risk; they may have low self-esteem, problems getting a job, and health insurance difficulties.

Q: Please tell us about the AST Pediatric Community of Practice Transition Workgroup. What is the makeup of the group and what are your goals and objectives?
A: This is a joint adult and pediatric transition workgroup, and its mission is to foster high-quality interdisciplinary transition practices for adolescent and young adult transplant recipients by facilitating access to evidence-based/expert transition guidelines and tools, collaborative transition research, transition education, and advocacy.

The workgroup is comprised of 50 to 60 transplant professionals and is interdisciplinary—we have adult and pediatric physicians, surgeons, nurses, psychologists, and other specialists. In addition to a core steering group, there are several subgroups in development that will work on a web-based transition toolkit, outcome assessment measures, identification of barriers, educational endeavors, and communications.
Top Ten Practice Pointers for Pediatric to Adult Transition

For pediatric providers
A timely start is very important.

1. Encourage parents to:
   • Actively involve their child in his/her health care from an early age, with progressive supervised participation.
   • Remain present as a coach, advisor, and confidante, even as they shift more responsibility to their child; studies have shown this is very important to foster adherence.
   • Cultivate habits of healthy active living from an early age. This will have lifelong benefits.

2. Proactively encourage regular school attendance and participation in peer-related social activities.
   • Be sensitive to the potential need for a neurocognitive assessment if there are any problems in school, since some children with early onset chronic illness may have specific learning deficits.

3. Begin formal transition preparation activities by the time the patient reaches 11 to 12 years of age.
   • Progressively increase the young person’s participation and self-management during health care appointments.
   • See the patient alone for part of each appointment starting at about age 14 years.
   • Spend time teaching the young person about his/her medical condition, since initial information was likely provided to the parents.
   • Encourage the patient to carry a concise personal medical summary such as a medical passport.
   • Promote development of self-advocacy skills.

4. Maintain an up-to-date succinct but comprehensive medical/surgical summary. This can serve as the foundation for the patient’s transfer document and help avoid last minute marathons of summarizing multivolume charts.

5. Incorporate transition readiness checklists into regularly scheduled care.
   • Formally assess the young person’s knowledge of his/her condition, skills in self-management, sense of responsibility, and communication/self-advocacy abilities at various stages of adolescence and make plans to work and follow-up on areas of weakness.
   • Do a final readiness assessment just prior to transfer.

6. Communicate early with the adult providers to whom the patient will transfer. Learn their clinic procedures and policies and their treatment protocols.
   • Consider shared or joint protocols to help avoid treatment changes shortly after transfer.
   • Arrange for a visit and tour of the adult center before the patient is transferred.

7. Shortly before the patient moves to adult care, ensure that the transfer summary is complete and up-to-date and includes all relevant history, treatments and procedures, consultants involved, important complications, medication intolerances, allergies, reports of special investigations, and any other important information.
   • Send the summary to the adult clinic prior to transfer.
   • Provide a succinct, easily understandable copy to the young person.
   • If possible, call or meet the adult team to discuss the patient’s health issues prior to transfer.
   • Communicate any problem areas in the final transition readiness checklist to the adult team at the time of transfer.

For adult providers
The process of transition to adult care doesn’t end at the time of transfer.

8. Try to develop an understanding of the phases of adolescent and emerging adult development, in particular the asynchronous timing of emotional development and executive function maturation.
   • Recall that fully developed executive functioning is not usually reached until the mid-20s and that young people may make seemingly rash decisions during periods of strong emotions.

9. Do your best to engage the young person, foster adherence, and promote his/her trust in the new health care system through more frequent appointments and monitoring, as well as discussion of potentially important young adult topics, such as school and work, family and friends, sexuality and birth control, and substance use.
   • Acknowledge the young person’s understanding and beliefs about his/her medical condition. He/she has likely lived for many years with these health issues.
   • Recognize that treatments used in pediatrics may be different from those in adult care and that pediatric onset conditions may have a different clinical trajectory than similar conditions beginning in adulthood.
   • Try not to make treatment changes shortly after transfer, to avoid confusion and potential lack of trust.

10. Be open with feedback to your pediatric colleagues about how their former patients are doing and suggestions about improving the transfer process.
Connect with top employers looking to hire you.

Attend the American Society of Nephrology (ASN) Kidney Week Career Fair at this year’s Annual Meeting to connect with top employers looking to hire ASN members! If you are unable to attend, simply upload your CV/resume on the ASN website and allow Career Fair employers to get in touch with you directly. Visit http://careers.asn-online.org.

Employers, space is limited so register as an exhibitor today.

To register your company as a Career Fair exhibitor e-mail Jim Cook at j.cook@jobtarget.com.

This event happens only once per year so don’t miss it!