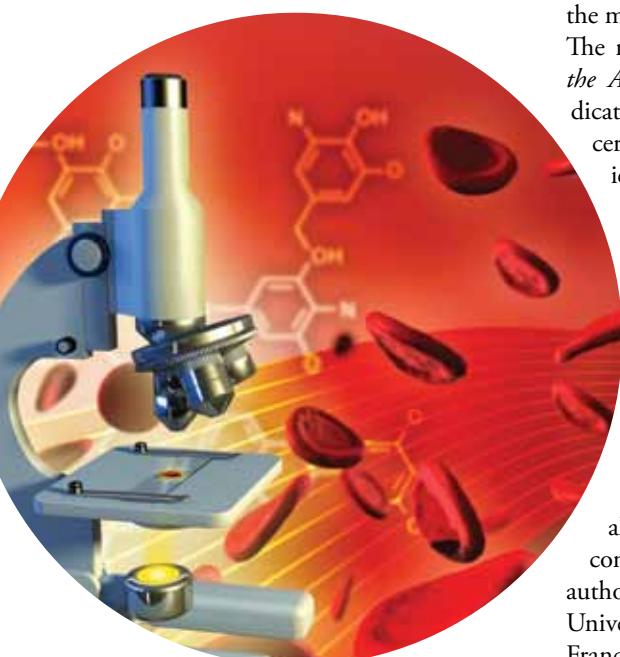


Kidney News

September 2012 | Vol. 4, Number 9

Serum Tests Reveal Severity of IgA Nephropathy



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 therapy."

Continued on page 4

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 physi-

cian 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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Diamond Level



Platinum Level



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

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

1. Medicare physicians	2. Practitioners	3. Therapists
Doctor of Medicine Doctor of Osteopathy Doctor of Podiatric Medicine Doctor of Optometry Doctor of Oral Surgery Doctor of Dental Medicine Doctor of Chiropractic	Physician Assistant Nurse Practitioner Clinical Nurse Specialist Certified Registered Nurse Anesthetist (and Anesthesiologist Assistant) Certified Nurse Midwife Clinical Social Worker Clinical Psychologist Registered Dietician Nutrition Professional Audiologist	Physical Therapist Occupational Therapist Qualified Speech-Language Therapist

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

Year	Successful PQRS Participation	Successful PQRS Participation + Extra MOC	No/Unsuccessful PQRS Participation
2010	+2.0%	—	No change
2011	+1.0%	+1.5%	No change
2012	+0.5%	+1.0%	No change
2013	+0.5%	+1.0%	No change in 2013 Based on 2013 reporting -1.5%
2014	+0.5%	+1.0%	No change in 2014 Based on 2014 reporting -2.0%
2015	No change	No change	
2016 onward	No change	No change	

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



To help ASN members meet the upcoming PQRS reporting requirement, the society is currently negotiating a contract with a CMS-qualified registry for PQRS reporting. ASN members will be able to report metrics for CMS-approved measures for 2012 and subsequent years at a special discounted rate by accessing a secure portal on the society's website. After users register and select the individual measures or measure group they want to report, the registry guides them through a few easy steps to rapidly collect and submit data to CMS for payment, much like online tax preparation software. As another courtesy to ASN members, technical assistance will be provided free of charge to users. Once the system goes live in October 2012, an alert will go out to ASN members with more information about signing up and using the software.

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. ●

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IgA Nephropathy

Continued from page 1

apy." Currently, assessment of disease severity is based partly on clinical and biochemical markers, such as proteinuria and the rate of loss of renal function, and partly on histologic features in kidney biopsy specimens, he said.

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; Hitoshi Suzuki, 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. When 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 paper is 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 pathology 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 Rossana Coppo, MD, who was not involved with the study and is the director of the nephrology, 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 Thibaudin, MD, Nicolas Maillard, MD, PhD, Christophe Mariat, MD, PhD (University Hospital of Saint-Etienne, France); Hiroyuki Yanagawa MD, PhD; Yasuhiko 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 <http://jasn.asnjournals.org/>; doi:10.1681/ASN.2012010053.



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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.

Journal View



Spot Urine Samples for Assessing Proteinuria in Suspected Pre-Eclampsia

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—73 percent of patients were considered frail. Even among patients younger than 40, the rate of frailty at the start of dialysis was 63 percent.

On 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, once 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, “Comprehensive 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].

Brief Summary of Prescribing Information for: OMONTYS (pEGINESATIDE) INJECTION FOR INTRAVENOUS OR SUBCUTANEOUS USE

WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE. See full prescribing information for complete boxed warning.

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 [see Warnings and Precautions].
- Use the lowest OMONTYS dose sufficient to reduce the need for red blood cell (RBC) transfusions [see Warnings and Precautions].

INDICATIONS AND USAGE

Anemia Due to Chronic Kidney Disease

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 [see Warnings and Precautions].
- 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 [see Warnings and Precautions].
- As a substitute for 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.

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 - 11.3 g/dL) (see Table 2), 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.
- 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 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 (CHOIR) and Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT)).

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

	NHS (N = 1265)	CHOIR (N = 1432)	TREAT (N = 4038)
Time Period of Trial	1993 to 1996	2003 to 2006	2004 to 2009
Population	Patients with CKD on hemodialysis with coexisting CHF or CAD, hematocrit $30 \pm 3\%$ on epoetin alfa	Patients with CKD not on dialysis with hemoglobin < 11 g/dL not previously administered epoetin alfa	Patients with CKD not on dialysis with type II diabetes, hemoglobin ≤ 11 g/dL
Hemoglobin Target; Higher vs. Lower (g/dL)	14.0 vs. 10.0	13.5 vs. 11.3	13.0 vs. ≥ 9.0
Median (Q1, Q3) Achieved Hemoglobin level (g/dL)	12.6 (11.6, 13.3) vs. 10.3 (10.0, 10.7)	13.0 (12.2, 13.4) vs. 11.4 (11.1, 11.6)	12.5 (12.0, 12.8) vs. 10.6 (9.9, 11.3)
Primary Endpoint	All-cause mortality or non-fatal MI	All-cause mortality, MI, hospitalization for CHF, or stroke	All-cause mortality, MI, myocardial ischemia, heart failure, and stroke
Hazard Ratio or Relative Risk (95% CI)	1.28 (1.06 – 1.56)	1.34 (1.03 – 1.74)	1.05 (0.94 – 1.17)
Adverse Outcome for Higher Target Group	All-cause mortality	All-cause mortality	Stroke
Hazard Ratio or Relative Risk (95% CI)	1.27 (1.04 – 1.54)	1.48 (0.97 – 2.27)	1.92 (1.38 – 2.68)

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 consisting of death, myocardial infarction, stroke, or serious adverse events of congestive heart failure, unstable angina or arrhythmia (hazard ratio 1.32, 95% CI: 0.97, 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 transfusions 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.

The safety and efficacy of OMONTYS have not been established for use in patients with anemia due to cancer chemotherapy. Results from clinical trials of ESAs in patients with anemia 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. 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 (e.g., iron deficiency, infection, inflammation, bleeding). If typical causes of lack or loss of hemoglobin response are excluded, evaluate the patient for the presence of antibodies to peginesatide. In the absence of antibodies to peginesatide, follow dosing recommendations for management of patients with an insufficient hemoglobin response to OMONTYS therapy.

Contact Affymax, Inc. (1-855-466-6689) to perform assays for binding and neutralizing antibodies.

Dialysis Management

Patients may require adjustments in their dialysis prescriptions after initiation of OMONTYS. 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%. 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 59 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 need-

ed 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 for detection of significant proteinuria or adverse pregnancy outcome in patients with suspected pre-eclampsia: systematic review and meta-analysis. *BMJ* 2012; 345:e4342].

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. Thereafter, 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 542 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 Caucasian, Black (including African Americans), and Asian patients were 57.9%, 37.4%, and 3.1%, respectively. The median weight adjusted dose of OMONTYS was 0.07mg/kg and 113 U/week/kg of epoetin.

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

Table 3 Adverse Reactions Occurring in $\geq 10\%$ of Dialysis Patients treated with OMONTYS

Adverse Reactions	Dialysis Patients Treated with OMONTYS (N = 1066)	Dialysis Patients Treated with Epoetin (N = 542)
Gastrointestinal Disorders		
Diarrhea	18.4%	15.9%
Nausea	17.4%	19.6%
Vomiting	15.3%	13.3%
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	18.4%	19.4%
Cough	15.9%	16.6%
Injury, Poisoning and Procedural Complications		
Arteriovenous Fistula Site Complication	16.1%	16.6%
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		
Hypotension	14.2%	14.6%
Hypertension	13.2%	11.4%
General Disorders and Administration Site Conditions		
Pyrexia	12.2%	14.0%
Metabolism and Nutrition Disorders		
Hyperkalemia	11.4%	11.8%
Infections and Infestations		
Upper Respiratory Tract Infection	11.0%	12.4%

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 premonitory 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 2357 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 (0.9%). 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 for anemia of CKD. 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 *in vitro* protein binding studies in rat, monkey and human sera. *In vitro* studies conducted with human hepatocytes or microsomes 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 polycythemia. OMONTYS should be used during pregnancy 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 stenoschisis, and variations in blood vessels) were mostly evident at doses of ≥ 10 mg/kg. The dose of 1 mg/kg results in exposures (AUC) comparable to those in humans after intravenous administration at a dose of 0.35 mg/kg in patients on dialysis. In a separate embryofetal developmental study in rats, reduced fetal weight and reduced ossification were seen at a lower dose of 0.25 mg/kg. Reduced fetal weight and delayed ossification in rabbits were observed at ≥ 0.5 mg/kg/dose of peginesatide. In a separate embryofetal developmental study in rabbits, adverse findings were observed at lower doses 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.

Geriatric Use

Of the total number of dialysis patients in Phase 3 clinical studies of OMONTYS, 32.5% were age 65 and over, while 13% were age 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

OVERDOSAGE

OMONTYS overdosage can elevate hemoglobin levels above the desired level, which should be managed with discontinuation or reduction of OMONTYS dosage and/or with phlebotomy, as clinically indicated. Cases of severe hypertension have been observed following overdose with ESAs [see Warnings and Precautions].

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

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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 standardized 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 combined equation 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].

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 inde-

pendence. 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 National 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 datasets.

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 devel-

opment until their mid-to-late 20s. Given these challenges, it may be difficult for the adolescent ESRD patient to cope with expectations of increased self-management and independence in the adult care system. Therefore, the high-risk period of adaptation to adult care may be a critical window during which intense support is warranted.

We can conclude that the relationships and interactions between age, graft-failure risk, and transfer of care are complex. In reviewing the current evidence it is difficult to distinguish graft-failure risk attributable to 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 multi-component interventions at the patient, provider, and system levels to optimize care for this group of patients. ●

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Nephrology Transition 101

By Miriam Kaufman, MD, FRCPC

Pediatric 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 transfer to adult 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%20Transition%20Program/33902-42487%20sign%20G2Go_Nephrology.pdf). Adapted from work done at Seattle Children's Hospital, the timeline can be distributed to parents at time of diagnosis, and it includes suggestions for promoting important skills in a number of domains, including social, self-care, education, and medical/health. The suggestions are aimed initially at parents caring for their young children during three key develop-

mental periods (ages 0 to 3, 4 to 7, and 8 to 11 years) and then shift to providing guidance to young people (ages 12 to 15 and 16 years and up). Many of the suggestions include practices that parents naturally follow with their healthy children but, in the interests of protecting their child with a kidney condition, might not pursue.

Ensuring knowledge of condition

Conversations about a child's medical condition are usually conducted with parents, and although the child is often present during these talks many children aren't capable of understanding the information or believe that it isn't important that they know it. This can discourage young people from developing a sense of ownership of their condition and their own health care. To move into the adult system, youth must have a basic understanding of their condition and their course through it, as well as an ability to describe important aspects to new health care providers. As children enter new phases in their lives—such as starting kindergarten, going into fourth grade, or junior high and high school—developmentally appropriate information should be reviewed with them. At age 12 or 13 years, they can learn a Three Sentence Summary (3SS) that will let them easily transmit information. The 3SS is similar to how medical trainees present a case to their staff, and can be reviewed and practiced a few times a year. Patients can also make a MyHealth Passport (<http://www.sickkids.ca/myhealthpassport>) with the assistance of a nurse or doctor. This online program allows patients or parents to easily enter their health information and then both print a wallet-sized card and save a PDF to store on their computer or other device. ●

Promoting self-management

Although parents often envision themselves as taking care of their child forever, it is important that young people take charge—as

much as possible—of their medication, diet, treatments, and other aspects of their care. Even children who have significant learning problems or cognitive delays can take responsibility for some of these issues. There is no gold standard for self-management in children yet, although some are using groups, online programs, and individual counseling to help young people become more responsible for their own care.

Introduction to the adult system

The fear of the unknown is common, and this can be exacerbated for children and parents who often hear from pediatric providers and patients that the adult system is a horrible place where parents will be ignored and young people are not welcome. Clearly, pediatric nephrologists need to be careful of what messages are conveyed to families. Having an introduction to adult providers and clinics before transfer can be extremely helpful in dispelling myths and “setting the stage” for new health care relationships. This can take the form of a joint clinic at the adult or pediatric clinic; a transition education event attended by members of both programs, patients, and families; or a virtual tour and introductions to adult providers.

Appropriate transfer procedures

Although transfer is but one point in the transition process, it is essential that a complete (yet succinct) medical, nursing, psychosocial, and pharmacological history is communicated to adult care providers, along with a copy for the young person. If possible, a verbal handover of information is invaluable, especially if the pediatric team can communicate some of the positives of the young person's personality or behavior. Young people should be given information about where the new clinic is, who to call in case of an emergency, and any other important details. Insurance issues need to be dealt with before the transfer. The transfer checklist used at the Hospital for Sick Children

fice. *Report to Congressional Requesters: End-Stage Renal Disease: Characteristics of Kidney Transplant Recipients, Frequency of Transplant Failures, and Cost to Medicare*. Washington, DC, Government Accountability Office, 2007

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can be found on the Good 2 Go Transition Program's website (<http://www.sickkids.ca/Good2Go/Transition-Interventions-Tools/Readiness-checklists/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 “babied” 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-s-t.org/content/ast-pcop-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 pediatrics. 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. ●

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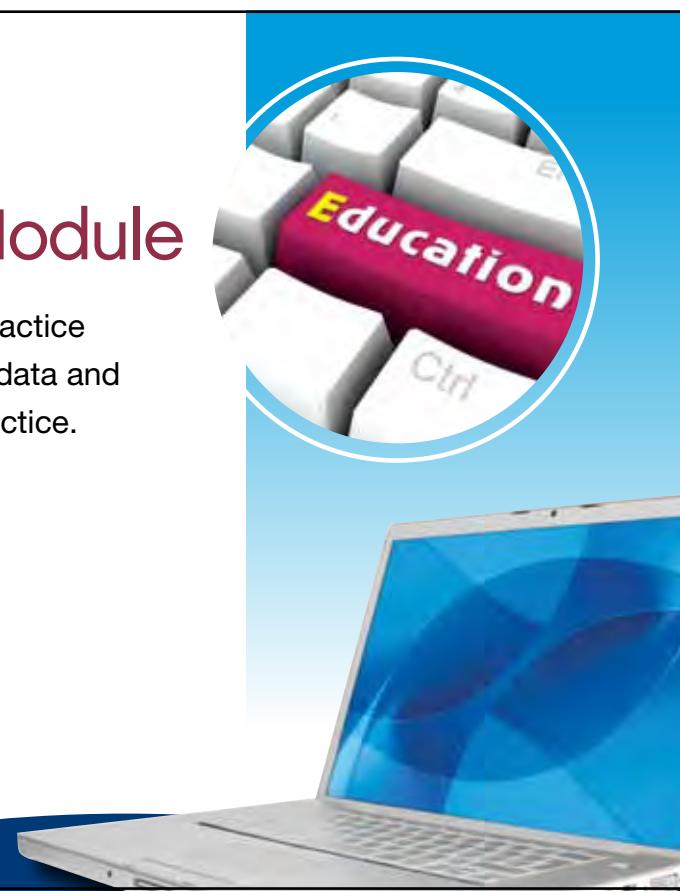
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Chronic Kidney Disease in Early Life: The Impact on Cognition, Education, and Workforce Integration

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 executive 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. ●

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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

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Optimizing Adherence

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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.

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The great divide—myth or reality? Adult physician perspectives

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 setting. 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 attuned to or understand their needs (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 it is unrealistic to expect the same relationship to develop immediately upon transfer to an adult practice.

Solutions through collaboration

How then can we improve the pediatric to adult transition process? Transition is a developmental process that should begin while patients are still in the pediatric setting and continue well beyond the transfer (8, 9). It would be helpful to conduct assessments of transition readiness and communicate concerns on both sides of the transition. At our institution an assessment of health care management skills is provided to all pediatric liver, and now kidney, 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 again shared with the adult team. Even 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 (12). 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. ●

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The Transition from Adolescent to Adult Care

Insurance Gaps—Bridging Troubled Waters

By Annette M. Oatt, Steven Steinberg, MD, and Dianne B. McKay, MD

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 23 years) (1). During the transition, the young patients often lose their health insurance coverage and this loss 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 (aged 19 to 25 years) did not have health insurance 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 often experience 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 impaired 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 aging-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 inpatient expenses, but there are deductibles 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 ESRD 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 Medicare unless they meet the criteria 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.

As for the states, Medicaid coverage is also problematic for the transitioning patient. Currently, many state Medicaid programs do not cover adults, and most young adults who are covered through Medicaid or the Children's Health Insurance Program lose their health insurance between the ages of 19 to 21 years because each state determines the last age of children's services. Medicaid covers hospital, physician, and medical costs, but it is dependent upon extremely low financial income and continuing eligibility (for those aged 65 years or older being blind or permanently disabled; under 21 years, being pregnant, in a skilled nursing facility, or a parent or caretaker of a child under 21). Since Medicaid can be reevaluated every few months, it cannot be counted on to provide for long-term support in this patient population.

The loss of health care coverage has obvious devastating consequences for a young adult transplant recipient and puts them at high risk for nonadherence and loss of graft function. As of 2010, insurance plans that included dependent coverage have changed their policy in order to cover adult children until their 26th birthday. This change in the insurance mandate has led to a dramatic increase in the numbers of insured young adults and has been an enormous help for young adults whose parents have health insurance (3).

Hope for those young adults transplant recipients who cannot join their parent's health plan will be provided by the ACA when it goes into effect in 2014, at which time they will have the opportunity to join subsidized private health plans even if their incomes are up to 400 percent of the federal poverty level (3). Yet problems will still exist for patients dependent upon Medicare due to their renal disease—although the Medicare income eligibility level has increased, the new health care provisions will not change other eligibility requirements for Medicare, such as the requirement to have worked for 10 years in Medicare-covered employment or have been a dependent of someone who has paid into Medicare (3).

Although the ACA has provided enormous help, there is no known provision in the ACA for extension of Medicare coverage for immunosuppressive drug coverage (7). This is a tremendous problem for young adults who often find it difficult to obtain a job with adequate benefits to cover the cost of their immunosuppressive medications. One solution for patients currently on Medicare is to recommend the patient for the Vocational Rehabilitation program, a return-to-work program available for any patient who has had a transplant and is eli-

gible for Medicare. The goal is to provide the young adult with skills that allow them to acquire employment that provides insurance coverage, although there are no guarantees they will find a job. Nevertheless, this should be considered in anticipation of the transition to the adult clinic.

The ACA does not provide coverage for undocumented transplant recipients, whose access to care can be particularly problematic. 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 insurability 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 success-

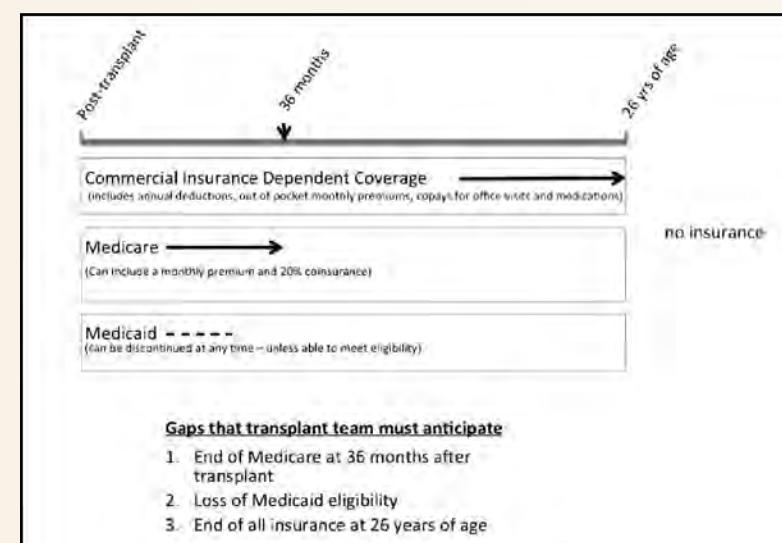
ful transfer of the patient to the adult setting. Additionally, health care providers must be active in public policy discussions to promote optimal insurability for this vulnerable patient population. ●

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Figure 1. Insurance coverage limits for the young adult kidney transplant recipient



Young Adult Clinics—Turning a Dream Into Reality

By Paul Harden, MB, ChB, FRCP

Managing young adult patients aged 16 to 30 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.

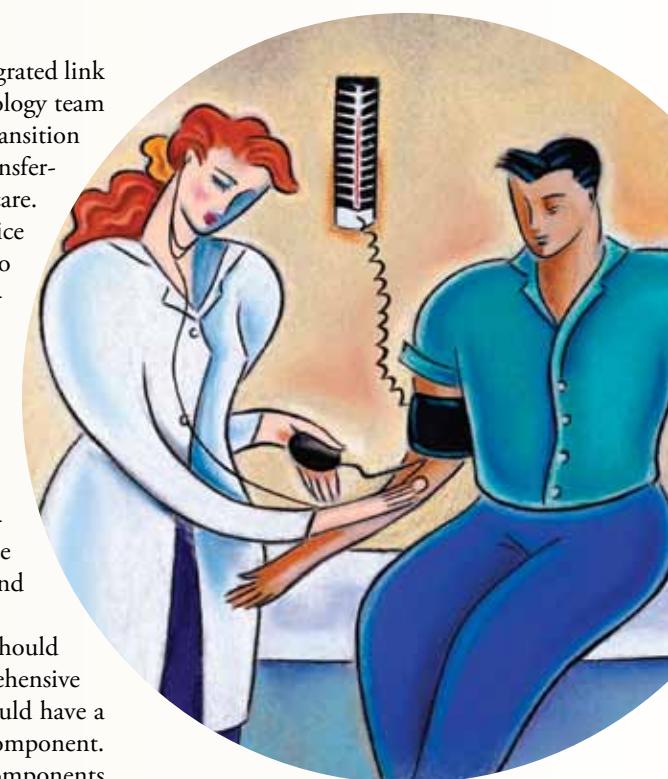
Young adult patients share little in common with most of the older patients within any kidney provider service and frequently, the multidisciplinary staff managing their care have difficulty engaging with this population. In feedback from questionnaires and focus groups young adult patients would prefer 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 once their individual medical consultations are completed. One ap-

proach 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.

sential 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.

Adult 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



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.

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 es-

improve immunosuppression adherence. Provision of separate social events such as group dining, activity weekends, and participation in the National Transplant Games can build a true group identity and substantially raise individual self-esteem. The result is the emergence of several key young adult patients who can act as mentors for new patients entering the clinic. If you are 17 years old and facing the prospect of ESRD the best person to give you advice on how dialysis or transplantation will affect your life is an experienced young adult patient, and frequently not a health care worker.

It will be a challenge to establish a young adult service as it requires a culture change within your nephrology unit to allow grouping all the young adult patients into a dedicated young adult service. Senior clinicians may not readily see the potential benefits and feel they are perfectly able to manage the care of such individuals. It is important to explain that existing health care models for this age group immerse

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. ●

Dr. Harden is affiliated with the University of Oxford, Oxford, UK.

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Industry Spotlight

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.

KAI-4169 drew attention at ASN Kidney Week in Philadelphia last November when it was reported that the drug had reduced parathyroid hormone by 33 percent in patients taking a 5-mg dose and by 49 percent in those taking a 10-mg dose. It is an experimental intravenous treatment for secondary hyperthyroidism in patients

For renal transplant patients

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Mycophenolate mofetil



Multiple companies offer a generic version of CellCept

- Currently, 11 different MMF tablets (500 mg) and 10 different MMF capsules (250 mg) are available.^{1,*}

myfortic



Produced only by Novartis:
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myfortic and CellCept or MMF should not be used interchangeably without physician supervision because the rate of absorption following the administration of these products is not equivalent.

Demonstrated efficacy and safety in *de novo* and maintenance renal transplant patients³⁻⁵

More than 81% of *myfortic* prescriptions^{†‡} had a \$0 co-pay with the Novartis Monthly Co-pay Card for eligible patients

Consistency also comes with savings:

Start your new *myfortic* patients with a 30-day free trial[§] by visiting www.myfortic.com or by calling the Novartis Transplant Reimbursement Access Point at 1-877-952-1000.

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*As of January 13, 2012.

[†]Based on data from the *myfortic* Co-pay Savings Program. Program is available to eligible patients taking *myfortic* and is subject to change without notice. Not valid for patients whose prescriptions are paid for by Medicare, Medicaid, or any other federally subsidized health care program, or for Massachusetts residents.

[‡]Initial prescription or refills based on 1-year transaction data (2011) for cash payment and insured patients combined.

[§]Product coverage and program subject to change without notice.

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 mofetil (MMF), or to any of its excipients

- *Embryofetal Toxicity:* *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. Amgen said patients with kidney disease often develop parathyroidism; this condition can worsen as kidney func-

tion declines. *Bloomberg Businessweek* noted in coverage of the acquisition.

Based in Thousand Oaks, CA, Amgen had total product sales in 2011 of \$15.3 billion and research and development expenses totaling \$3.2 billion. In March, Omontys (pigesentide, 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. Amgen 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-4169 does not have the adverse gastrointestinal events seen in 20 percent to 30 percent of patients taking Sensipar," *BioWorld* noted. ●

Important Safety Information: (cont)

- **Pregnancy Exposure Prevention and Planning:** FRP must be made aware of the increased risk of first trimester pregnancy loss and congenital malformations, and must be counseled regarding pregnancy prevention and planning. (See additional important Pregnancy Testing, Contraception, and Pregnancy Planning information below)
- **Lymphoma and Other Malignancies:** Patients receiving immunosuppressive regimens involving combinations of drugs, including *myfortic*, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin
- **Infections:** Oversuppression of the immune system can also increase susceptibility to infection, fatal infections, and sepsis
- **Polyomavirus Infections:** Immunosuppressed patients are at increased risk for opportunistic infections, including Polyomavirus infections. Polyomavirus infections in transplant patients may have serious and sometimes fatal outcomes. These include cases of JC virus-associated progressive multifocal leukoencephalopathy (PML) and Polyomavirus-associated nephropathy (PVAN), especially due to BK virus infections, which have been observed in patients receiving *myfortic*. PVAN, especially due to BK virus infection, is associated with serious outcomes, including deteriorating renal function and renal graft loss. Patient monitoring may help detect patients at risk for PVAN
- Cases of PML have been reported in patients treated with MPA derivatives including MMF and mycophenolate sodium. PML, which is sometimes fatal, commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies, and ataxia. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms, and consultation with a neurologist should be considered as clinically indicated. Reduction in immunosuppression should be considered for patients who develop evidence of PML or PVAN. Physicians should also consider the risk that reduced immunosuppression represents to the graft
- **Blood Dyscrasias Including Pure Red Cell Aplasia:** Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA in combination with other immunosuppressive agents. In some cases, PRCA was found to be reversible with dose reduction or cessation of therapy with MPA derivatives. In transplant patients, however, reduced immunosuppression may place the graft at risk. Patients receiving *myfortic* should be monitored for blood dyscrasias (eg, neutropenia or anemia). If blood dyscrasias occur (eg, neutropenia develops [ANC <1.3 x 10³/µL or anemia]), dosing with *myfortic* should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately
- **Pregnancy Testing:** To prevent unplanned exposure during pregnancy, FRP should have a serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL immediately before starting *myfortic*. Another pregnancy test with the same sensitivity should be done 8 to 10 days later. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient. In the event of a positive pregnancy test, females should be counseled with regard to whether the maternal benefits of mycophenolate treatment may outweigh the risks to the fetus in certain situations
- **Contraception:** FRP taking *myfortic* must receive contraceptive counseling and use acceptable contraception during the entire *myfortic* therapy, and for 6 weeks after stopping *myfortic*, unless the patient chooses abstinence. Patients should be aware that *myfortic* reduces blood levels of the hormones in the oral contraceptive pill, and could theoretically reduce its effectiveness. (Please see package insert for acceptable contraceptive methods for females)
- **Pregnancy Planning:** For patients who are considering pregnancy, consider alternative immunosuppressants with less potential for embryofetal toxicity. Risks and benefits of *myfortic* should be discussed with the patient
- **Gastrointestinal Disorders:** Gastrointestinal bleeding (requiring hospitalization) has been reported in *de novo* renal transplant patients (1.0%) and maintenance patients (1.3%) treated with *myfortic* (up to 12 months)
- **Patients with Renal Impairment:** Subjects with severe chronic renal impairment (GFR <25 mL/min/1.73 m²) may present higher plasma MPA and MPAG AUC relative to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data are available on the safety of long-term exposure to these levels of MPAG
- **Concomitant Medications:** Caution should be used with drugs that interfere with enterohepatic recirculation because of the potential to reduce efficacy
- **Hypoxanthine-guanine phosphoribosyl-transferase (HPRT) Deficiency:** *myfortic* should be avoided in patients with HPRT deficiency such as Lesch-Nyhan and Kelley-Seegmiller syndrome
- **Immunizations:** Use of live attenuated vaccines should be avoided
- The principal adverse reactions associated with the administration of *myfortic* include constipation, nausea, and urinary tract infection in *de novo* patients and nausea, diarrhea, and nasopharyngitis in maintenance patients

References: 1. FDA approved drug products: mycophenolate mofetil. Drugs@FDA Web site. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_drug_name. Updated January 13, 2012. Accessed May 11, 2012. 2. Data on file. IMS Health, National Prescription Audit TRx Data: January 2011 to January 2012. 3. Salvadori M, Holzer H, de Mattos A, et al; on behalf of ERL B301 Study Groups. Enteric-coated mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in *de novo* renal transplant patients. *Am J Transplant*. 2004;4(2):231-236. 4. *Myfortic*® (mycophenolic acid*) delayed-release tablets *as mycophenolate sodium prescribing information. East Hanover, NJ: Novartis Pharmaceuticals Corp.; June 2012. 5. Budde K, Knoll G, Curtis J, et al; on behalf of ERL B302 Study Group. Long-term safety and efficacy after conversion of maintenance renal transplant recipients from mycophenolate mofetil (MMF) to enteric-coated mycophenolate sodium (EC-MPA, *myfortic*®). *Clin Nephrol*. 2006;66(2):103-111.

Please see Brief Summary of Prescribing Information, including **Boxed WARNINGS**, on adjacent pages.



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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 triggered 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 808 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, Feraheme's net 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. ●

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 per 1.73 m² to receive calcium acetate, lanthanum carbonate, sevelamer carbonate, or placebo. The primary endpoint was 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 associ-

Myfortic® (mycophenolic acid*) delayed-release tablets *as mycophenolate sodium

Rx only

BRIEF SUMMARY: Please see package insert for full prescribing 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. (see **WARNINGS** and **PRECAUTIONS**)

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 use Myfortic® (mycophenolic acid). 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. (see **WARNINGS** and **PRECAUTIONS**)

INDICATIONS AND USAGE

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

CONTRAINdications

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

WARNINGS (SEE BOXED WARNING) EMBRYOFETAL TOXICITY

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, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney (see **PRECAUTIONS: Pregnancy**).

Pregnancy Exposure Prevention and Planning

Females of reproductive potential must be made aware of the increased risk of first trimester pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention and planning. For recommended pregnancy testing and contraception methods (see **PRECAUTIONS: Pregnancy Exposure Prevention and Planning**).

Lymphoma and Other Malignancies

Patients receiving immunosuppressive regimens involving combinations of drugs, including Myfortic® (mycophenolic acid), as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see **ADVERSE REACTIONS**). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

The rates for lymphoproliferative disease or lymphoma in Myfortic-treated patients were comparable to the mycophenolate mofetil group in the *de novo* and maintenance studies (see **ADVERSE REACTIONS**). As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Infections

Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis. Fatal infections can occur in patients receiving immunosuppressive therapy (see **ADVERSE REACTIONS**).

Polyomavirus Infection

Patients receiving immunosuppressants, including Myfortic are at increased risk for opportunistic infections, including Polyomavirus infections. Polyomavirus infections in transplant patients may have serious, and sometimes, fatal outcomes. These include cases of JC virus associated progressive multifocal leukoencephalopathy (PML) and Polyomavirus associated nephropathy (PVAN) especially due to BK virus infection which have been observed in patients receiving Myfortic.

PVAN, especially due to BK virus infection, is associated with serious outcomes, including deteriorating renal function and renal graft loss (see **ADVERSE REACTIONS**). Patient monitoring may help detect patients at risk for PVAN.

Cases of PML have been reported in patients treated with MPA derivatives which include mycophenolate mofetil (MMF) and mycophenolate sodium (see **ADVERSE REACTIONS**). PML, which is sometimes fatal, commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies and ataxia. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consult with a neurologist should be considered as clinically indicated.

Reduction in immunosuppression should be considered for patients who develop evidence of PML or PVAN. Physicians should also consider the risk that reduced immunosuppression represents to the functioning allograft.

Blood Dyscrasias Including Pure Red Cell Aplasia

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolic acid (MPA) derivatives in combination with other immunosuppressive agents. The mechanism for MPA derivatives induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppressive regimen is also unknown. In some cases PRCA was found to be reversible with dose reduction or cessation of therapy with MPA derivatives. In transplant patients, however, reduced immunosuppression may place the graft at risk. Changes to Myfortic therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimize the risk of graft rejection (see **ADVERSE REACTIONS**, **Post-marketing Experience**).

Patients receiving Myfortic should be monitored for blood dyscrasias (e.g. neutropenia or anemia (see **PRECAUTIONS, Laboratory Tests**). The development of neutropenia may be related to Myfortic itself, concomitant medications, viral infections, or some combination of these events. If blood dyscrasias occur (e.g. neutropenia (ANC <1.3x10⁹/µL or anemia), dosing with Myfortic should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately (see **DOSAGE AND ADMINISTRATION** in the full prescribing information).

Patients receiving Myfortic should be instructed to immediately report any evidence of infection, unexpected bruising, bleeding, or any other manifestation of bone marrow suppression.

Concomitant Use

Myfortic has been administered in combination with the following agents in clinical trials: antithymocyte/lymphocyte immunoglobulin, muromonab-CD3, basiliximab, daclizumab, cyclosporine, and corticosteroids. The efficacy and safety of Myfortic in combination with other immunosuppression agents have not been determined.

PRECAUTIONS

Pregnancy Exposure Prevention and Planning

Females of reproductive potential must be made aware of the increased risk of first trimester pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention and planning.

Females of reproductive potential include girls who have entered puberty and all women who have a uterus and have not passed through menopause. Menopause is the permanent end of menstruation and fertility. Menopause should be clinically confirmed by a patient's healthcare practitioner. Some commonly used diagnostic criteria include 1) 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or 2) post-surgical from a bilateral oophorectomy.

Pregnancy Testing

To prevent unplanned exposure during pregnancy, females of reproductive potential should have a serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL immediately before starting Myfortic. Another pregnancy test with the same sensitivity should be done 8 to 10 days later. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient.

In the event of a positive pregnancy test, females should be counseled with regard to whether the maternal benefits of mycophenolate treatment may outweigh the risks to the fetus in certain situations.

Contraception

Females of reproductive potential taking Myfortic must receive contraceptive counseling and use acceptable contraception (see **Table 4 for Acceptable Contraception Methods**). Patients must use acceptable birth control during entire Myfortic therapy, and for 6 weeks after stopping Myfortic, unless the patient chooses abstinence (she chooses to avoid heterosexual intercourse completely).

Patients should be aware that Myfortic reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness (see **PRECAUTIONS: Information for Patients and PRECAUTIONS: Drug Interactions: Oral Contraceptives**).

Table 4 Acceptable Contraception Methods for Females of Reproductive Potential

Pick from the following birth control options:

Option 1		
Methods to Use Alone	Intrauterine devices (IUDs)	Tubal sterilization
OR		
Option 2	Hormone Methods choose 1	Barrier Methods choose 1
Choose One Hormone Method AND One Barrier Method	Estrogen and Progesterone Oral Contraceptive Pill Transdermal patch Vaginal ring Progesterone-only Injection Implant	Diaphragm with spermicide Cervical cap with spermicide Contraceptive sponge Male condom Female condom
OR		
Option 3	Barrier Methods choose 1	Barrier Methods choose 1
Choose One Barrier Method from each column (must choose two methods)	Diaphragm with spermicide Cervical cap with spermicide Contraceptive sponge	Male condom Female condom

Pregnancy Planning

For patients who are considering pregnancy, consider alternative immunosuppressants with less potential for embryofetal toxicity. Risks and benefits of Myfortic should be discussed with the patient.

Gastrointestinal Disorders

Gastrointestinal bleeding (requiring hospitalization) has been reported in *de novo* renal transplant patients (1.0%) and maintenance patients (1.3%) treated with Myfortic® (mycophenolic acid) (up to 12 months). Intestinal perforations, gastrointestinal hemorrhage, gastric ulcers and duodenal ulcers have rarely been observed. Most patients receiving Myfortic were also receiving other drugs known to be associated with these complications. Patients with active peptic ulcer disease were excluded from enrollment in studies with Myfortic. Because MPA derivatives have been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage, and perforation, Myfortic should be administered with caution in patients with active serious digestive system disease (see **ADVERSE REACTIONS**).

Patients with Renal Impairment

Subjects with severe chronic renal impairment (GFR <25 mL/min/1.73 m²) may present higher plasma MPA and MPAG AUCs relative to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data are available on the safety of long-term exposure to these levels of MPAG.

In the *de novo* study, 18.3% of Myfortic patients versus 16.7% in the mycophenolate mofetil group experienced delayed graft function (DGF). Although patients with DGF experienced a higher incidence of certain adverse events (anemia, leukopenia, and hyperkalemia) than patients without DGF, these events in DGF patients were not more frequent in patients receiving Myfortic compared to mycophenolate mofetil. No dose adjustment is recommended for these patients; however, such patients should be carefully observed (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION** in the full prescribing information).

Concomitant Medications

In view of the significant reduction in the AUC of MPA by cholestyramine when administered with mycophenolate mofetil, caution should be used in the concomitant administration of Myfortic with drugs that interfere with enterohepatic recirculation because of the potential to reduce the efficacy (see **PRECAUTIONS, Drug Interactions**).

ated with progression of kidney disease, left ventricular hypertrophy, and all-cause mortality. Active therapy significantly increased calcification of the coronary arteries and abdominal aorta (coronary: median increases of 18.1 percent versus 0.6 percent; abdominal aorta: median increases of 15.4 percent versus 3.4 percent). "There appeared to be substantial differences among the three different phosphate binders on the progression of vascular calcification and on levels of fibroblast growth factor 23; however the trial was not powered to examine specific binders versus placebo nor versus each other," said Block.

Future of phosphate binders in patients with CKD

The results reveal that treatment with phosphate binders can significantly lower urinary phosphorus levels, moderately lower blood phosphorus levels, and slow the progression of secondary hyperparathyroidism in patients with CKD who have normal or near-normal levels of serum phosphorus. Despite these positive effects, phosphate binders do not seem to have any effect on the blood levels of a hormone that regulates phosphate excretion in the urine, and the drugs cause

vascular calcification, which can lead to heart problems. Heart disease is the leading cause of death in patients with CKD.

"It was our expectation that effective reductions in phosphorus absorption would lower serum phosphorus more substantially, result in a reduction of fibroblast growth factor 23 levels, result in an increase in endogenous 1-25 vitamin D3 levels, and attenuate the progression of calcification relative to placebo in patients who were already calcified," Block said. "In all of these areas our results contradicted our expectations." The increased calcification observed in the

study was seen not only in patients receiving calcium-containing phosphate binders, suggesting that phosphate binding therapy may have adverse health consequences not previously recognized in the short-term clinical trials used for approval.

These findings call into question the safety and effectiveness of phosphate binders in patients with CKD.

"While we continue to believe that serum phosphorus is a key component of the increased cardiovascular risk associated with kidney disease, our results suggest the use of the currently approved phosphate binding drugs does not result in substantial reductions in serum phosphorus and may be associated with harm in this population," said Block.

Csaba Kovesdy, MD, who is the Fred Hatch Professor of Medicine in Nephrology at the University of Tennessee Health Science Center, in Memphis, said that the results regarding the biochemical effects of the binders are not surprising, but the effects on vascular calcification are more difficult to interpret.

"The results of this study should not be used to conclude that phosphorus binders are harmful. The study was not powered to assess changes in vascular calcification, and only 81 patients (55 percent of the total enrolled) were assessed for changes in this end point," he said. Kovesdy, who was not involved with the study, added that because it is unclear how the baseline characteristics of these 81 patients differed from one another, it is possible that patients in the phosphate binder arm had baseline characteristics that predisposed them to more progressive calcification independently of treatment.

Tamara Isakova, MD, an assistant professor at the University of Miami Miller School of Medicine and an expert in mineral metabolism abnormalities in CKD, noted that additional studies, including those that investigate alternatives to phosphate binders, are needed. "The report by Dr. Block et al. and other recent studies should further motivate the nephrology community to continue to define the safety and efficacy of binders in CKD and to further investigate the role of dietary phosphate restriction as a potentially safe and effective sole or adjunctive risk-reduction strategy in this population," she said.

Myfortic® (mycophenolic acid*) delayed-release tablets *as mycophenolate sodium

Patients with HGprt Deficiency

On theoretical grounds, because Myfortic is an IMPDH Inhibitor, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGprt) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Immunizations

During treatment with Myfortic, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective (see PRECAUTIONS, Drug Interactions, Live Vaccines).

Laboratory Tests

Complete blood count should be performed weekly during the first month, twice monthly for the second and the third month of treatment, then monthly through the first year. If neutropenia develops ($ANC < 1.3 \times 10^3/\mu L$), dosing with Myfortic should be interrupted or the dose reduced, appropriate tests performed, and the patient managed accordingly (see WARNINGS).

Drug Interactions

The following drug interaction studies have been conducted with Myfortic:

Gastroprotective agents

Antacids with magnesium and aluminum hydroxides:

Absorption of a single dose of Myfortic was decreased when administered to 12 stable renal transplant patients also taking magnesium-aluminum-containing antacids (30 mL); the mean C_{max} and $AUC_{(0-1)}$ values for MPA were 25% and 37% lower, respectively, than when Myfortic was administered alone under fasting conditions. It is recommended that Myfortic and antacids not be administered simultaneously.

Proton Pump Inhibitors:

In a study conducted in 12 healthy volunteers, the pharmacokinetics of MPA were observed to be similar when a single dose of 720 mg Myfortic was administered alone and following concomitant administration of Myfortic and pantoprazole, which was administered at a dose of 40 mg BID for 4 days.

Cyclosporine: When studied in stable renal transplant patients, cyclosporine, USP (MODIFIED) pharmacokinetics were unaffected by steady-state dosing of Myfortic.

The following recommendations are derived from drug interaction studies conducted following the administration of mycophenolate mofetil:

Acyclovir/Ganciclovir: May be taken with Myfortic; however, during the period of treatment, physicians should monitor blood cell counts. Both acyclovir/ganciclovir and MPAG concentrations are increased in the presence of renal impairment, their coexistence may compete for tubular secretion and further increase in the concentrations of the two.

Azathioprine/Mycophenolate Mofetil: Given that azathioprine and mycophenolate mofetil inhibit purine metabolism, it is recommended that Myfortic not be administered concomitantly with azathioprine or mycophenolate mofetil.

Cholestyramine and Drugs that Bind Bile Acids: These drugs interrupt enterohepatic recirculation and reduce MPA exposure when coadministered with mycophenolate mofetil. Therefore, do not administer Myfortic with cholestyramine or other agents that may interfere with enterohepatic recirculation or drugs that may bind bile acids, for example bile acid sequestrates or oral activated charcoal, because of the potential to reduce the efficacy of Myfortic.

Oral Contraceptives: In a drug-drug interaction study, mean levonorgestrel AUC was decreased by 15% when coadministered with mycophenolate mofetil. Although Myfortic may not have any influence on the ovulation-suppressing action of oral contraceptives, it is recommended to co-administer Myfortic with hormonal contraceptives, (e.g. birth control pill, transdermal patch, vaginal ring, injection, and implant) with caution and additional barrier contraceptive methods must be used. (see PRECAUTIONS: Pregnancy Exposure Prevention and Planning).

Live Vaccines: During treatment with Myfortic, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective. Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination (see PRECAUTIONS, General).

Drugs that alter the gastrointestinal flora may interact with Myfortic by disrupting enterohepatic recirculation. Interference of MPAG hydrolysis may lead to less MPA available for absorption.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week oral carcinogenicity study in rats, mycophenolate sodium was not tumorigenic at daily doses up to 9 mg/kg, the highest dose tested. This dose resulted in approximately 0.6-1.2 times the systemic exposure (based upon plasma AUC) observed in renal transplant patients at the recommended dose of 1.44 g/day. Similar results were observed in a parallel study in rats performed with mycophenolate mofetil. In a 104-week oral carcinogenicity study in mice, mycophenolate mofetil was not tumorigenic at a daily dose level as high as 180 mg/kg (which corresponds to 0.6 times the proposed mycophenolate sodium therapeutic dose based upon body surface area).

The genotoxic potential of mycophenolate sodium was determined in five assays. Mycophenolate sodium was genotoxic in the mouse lymphoma/thymidine kinase assay, the micronucleus test in V79 Chinese hamster cells, and the *in-vivo* mouse micronucleus assay. Mycophenolate sodium was not genotoxic in the bacterial mutation assay (*Salmonella typhimurium* TA 1535, 97a, 98, 100, & 102) or the chromosomal aberration assay in human lymphocytes. Mycophenolate mofetil generated similar genotoxic activity. The genotoxic activity of MPA is probably due to the depletion of the nucleotide pool required for DNA synthesis as a result of the pharmacodynamic mode of action of MPA (inhibition of nucleotide synthesis).

Mycophenolate sodium had no effect on male rat fertility at daily oral doses as high as 18 mg/kg and exhibited no testicular or spermatogenic effects at daily oral doses of 20 mg/kg for 13 weeks (approximately two-fold the therapeutic systemic exposure of MPA). No effects on female fertility were seen up to a daily dose of 20 mg/kg, which was approximately three-fold higher than the recommended therapeutic dose based upon systemic exposure.

Pregnancy

Pregnancy Category D (See WARNINGS)

Following oral or IV administration, MMF is metabolized to mycophenolic acid (MPA), the active ingredient in Myfortic and the active form of the drug. Use of MMF 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 cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney. In animal studies, congenital malformations and pregnancy loss occurred when pregnant rats and rabbits received mycophenolic acid at dose multiples similar to and less than clinical doses. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Risks and benefits of Myfortic should be discussed with the patient. When appropriate, consider alternative immunosuppressants with less potential for embryofetal toxicity. In certain situations, the patient and her healthcare practitioner may decide that the maternal benefits outweigh the risks to the fetus. For those females using Myfortic at any time during pregnancy and those becoming pregnant within 6 weeks of discontinuing therapy, the healthcare practitioner should report the pregnancy to the Mycophenolate Pregnancy Registry (1-800-617-8191). The healthcare practitioner should strongly encourage the patient to enroll in the pregnancy registry. The information provided to the registry will help the Health Care Community to better understand the effects of mycophenolate in pregnancy.

In the National Transplantation Pregnancy Registry (NTPR), there were data on 33 MMF-exposed pregnancies in 24 transplant patients; there were 15 spontaneous abortions (45%) and 18 live-born infants. Four of these 18 infants had structural malformations (22%). In postmarketing data (collected from 1995 to 2007) on 77 women exposed to systemic MMF during pregnancy, 25 had spontaneous abortions and 14 had a malformed infant or fetus. Six of 14 malformed offspring had ear abnormalities. Because these postmarketing data are reported voluntarily, it is not always possible to reliably estimate the frequency of particular adverse outcomes. These malformations are similar to findings in animal reproductive toxicology studies. For comparison, the background rate for congenital anomalies in the United States is about 3%, and NTPR data show a rate of 4-5% among babies born to organ transplant patients using other immunosuppressive drugs. There are no relevant qualitative or quantitative differences in the teratogenic potential of mycophenolate sodium and mycophenolate mofetil.

In a teratology study performed with mycophenolate sodium in rats, at a dose as low as 1 mg/kg, malformations in the offspring were observed, including anophthalmia, exencephaly and umbilical hernia. The systemic exposure at this dose represents 0.05 times the clinical exposure at the dose of 1.44 g/day Myfortic. In teratology studies in rabbits, fetal resorptions and malformations occurred from 80 mg/kg/day, in the absence of maternal toxicity (dose levels are equivalent to about 0.8 times the recommended clinical dose, corrected for BSA).

Nursing Mothers

It is not known whether MPA is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from MPA, a decision should be made whether to discontinue the drug or to discontinue nursing while on treatment or within 6 weeks after stopping therapy, taking into account the importance of the drug to the mother.

Pediatric Use

De novo Renal Transplant

The safety and effectiveness of Myfortic in *de novo* pediatric renal transplant patients have not been established.

Stable Renal Transplant
There are no pharmacokinetic data available for pediatric patients <5 years. The safety and effectiveness of Myfortic have been established in the age group 5-16 years in stable pediatric renal transplant patients. Use of Myfortic in this age group is supported by evidence from adequate and well-controlled studies of Myfortic in stable adult renal transplant patients. Limited pharmacokinetic data are available for stable pediatric renal transplant patients in the age group 5-16 years. Pediatric doses for patients with BSA <1.19 m² cannot be accurately administered using currently available formulations of Myfortic tablets (see CLINICAL PHARMACOLOGY, Special Populations and DOSAGE AND ADMINISTRATION in the full prescribing information).

Geriatric Use

Patients ≥65 years may generally be at increased risk of adverse drug reactions due to immunosuppression. Clinical studies of Myfortic did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The incidence of adverse events for Myfortic® (mycophenolic acid) was determined in randomized, comparative, active-controlled, double-blind, double-dummy trials in prevention of acute rejection in *de novo* and maintenance kidney transplant patients.

The principal adverse reactions associated with the administration of Myfortic include constipation, nausea, and urinary tract infection in *de novo* patients and nausea, diarrhea and nasopharyngitis in maintenance patients. Adverse events reported in ≥20% of patients receiving Myfortic or mycophenolate mofetil in the 12-month *de novo* renal study and maintenance renal study, when used in combination with cyclosporine, USP (MODIFIED) and corticosteroids, are listed in Table 5. Adverse event rates were similar between Myfortic and mycophenolate mofetil in both *de novo* and maintenance patients.

Table 5. Adverse Events (%) in Controlled *de novo* and Maintenance Renal Studies Reported in ≥20% of Patients

	<i>de novo</i> Renal Study		Maintenance Renal Study	
	Myfortic® 1.44 g/day (n=213)	mycophenolate mofetil 2 g/day (n=210)	Myfortic® 1.44 g/day (n=159)	mycophenolate mofetil 2 g/day (n=163)
Blood and Lymphatic System Disorders				
Anemia	21.6	21.9	—	—
Leukopenia	19.2	20.5	—	—
Gastrointestinal System Disorders				
Constipation	38.0	39.5	—	—
Nausea	29.1	27.1	24.5	19.0
Diarrhea	23.5	24.8	21.4	24.5
Vomiting	23.0	20.0	—	—
Dyspepsia	22.5	19.0	—	—
Infections and Infestations				
Urinary Tract Infection	29.1	33.3	—	—
CMV Infection	20.2	18.1	—	—
Nervous System Disorder				
Insomnia	23.5	23.8	—	—
Surgical and Medical Procedure				
Postoperative Pain	23.9	18.6	—	—

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 Smits, PhD, Andrew N. Hoofnagle, MD, PhD, Laura Kooienga, MD, Ravi Thadhani, MD, Michael Mannstadt, MD, Myles Wolf, MD, and Glenn M. Chertow, MD.

The article, entitled "A randomized trial of phosphate binders in patients with moderate chronic kidney disease," is available online at <http://jasn.asnjournals.org/>; doi: 10.1681/ASN.2012030223.

Policy Update

Fall 2012 Congressional Spotlight

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 showdown over 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 will still have its 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 total amount of money the government is allowed to borrow), which 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/.

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Table 6 summarizes the incidence of opportunistic infections in *de novo* and maintenance transplant patients, which were similar in both treatment groups.

Table 6 Viral and Fungal Infections (%) Reported Over 0-12 Months

	<i>de novo</i> Renal Study Myfortic® 1.44 g/day (n = 213)	Maintenance Renal Study mofetil 2 g/day (n = 210)	<i>de novo</i> Renal Study Myfortic® 1.44 g/day (n = 159)	Maintenance Renal Study mofetil 2 g/day (n = 163)
(%)	(%)	(%)	(%)	(%)
Any Cytomegalovirus	21.6	20.5	1.9	1.8
- Cytomegalovirus Disease	4.7	4.3	0	0.6
Herpes Simplex	8.0	6.2	1.3	2.5
Herpes Zoster	4.7	3.8	1.9	3.1
Any Fungal Infection	10.8	11.9	2.5	1.8
- Candida NOS	5.6	6.2	0	1.8
- Candida Albicans	2.3	3.8	0.6	0

The following opportunistic infections occurred rarely in the above controlled trials: aspergillus and cryptococcus.

The incidence of malignancies and lymphoma is consistent with that reported in the literature for this patient population. Lymphoma developed in 2 *de novo* patients (0.9%), (one diagnosed 9 days after treatment initiation) and in 2 maintenance patients (1.3%) (one was AIDS-related), receiving Myfortic with other immunosuppressive agents in the 12-month controlled clinical trials. Nonmelanoma skin carcinoma occurred in 0.9% *de novo* and 1.8% maintenance patients. Other types of malignancy occurred in 0.5% *de novo* and 0.6% maintenance patients.

The following adverse events were reported between 3% to <20% incidence in *de novo* and maintenance patients treated with Myfortic in combination with cyclosporine and corticosteroids are listed in Table 7.

Table 7 Adverse Events Reported in 3% to <20% of Patients Treated with Myfortic® in Combination with Cyclosporine* and Corticosteroids

	<i>de novo</i> Renal Study	Maintenance Renal Study
Blood and Lymphatic Disorders	Lymphocytopenia, thrombocytopenia	Leukopenia, anemia
Cardiac Disorder	Tachycardia	—
Eye Disorder	Vision blurred	—
Endocrine Disorders	Cushingoid, hirsutism	—
Gastrointestinal Disorders	Abdominal pain upper, flatulence, abdominal distension, sore throat, abdominal pain lower, abdominal pain, gingival hyperplasia, loose stool	Vomiting, dyspepsia, abdominal pain, constipation, gastroesophageal reflux disease, loose stool, flatulence, abdominal pain upper
General Disorders and Administration Site Conditions	Edema, edema lower limb, pyrexia, pain, fatigue, edema peripheral, chest pain	Fatigue, pyrexia, edema, chest pain, peripheral edema
Infections and Infestations	Nasopharyngitis, herpes simplex, upper respiratory tract infection, oral candidiasis, herpes zoster, sinusitis, wound infection, implant infection, pneumonia	Nasopharyngitis, upper respiratory tract infection, urinary tract infection, influenza, sinusitis
Injury, Poisoning, and Procedural Complications	Drug toxicity	Postprocedural pain
Investigations	Blood creatinine increased, hemoglobin decrease, blood pressure increased, liver function tests abnormal	Blood creatinine increase, weight increase
Metabolism and Nutrition Disorders	Hypocalcemia, hyperuricemia, hyperlipidemia, hypokalemia, hypophosphatemia, hypercholesterolemia, hyperkalemia, hypomagnesemia, diabetes mellitus, hyperphosphatemia, dehydration, fluid overload, hyperglycemia, hypercalcemia	Dehydration, hypokalemia, hypercholesterolemia
Musculoskeletal and Connective Tissue Disorders	Back pain, arthralgia, pain in limb, muscle cramps, myalgia	Arthralgia, pain in limb, back pain, muscle cramps, peripheral swelling, myalgia
Nervous System Disorders	Tremor, headache, dizziness (excluding vertigo)	Headache, dizziness
Psychiatric Disorders	Anxiety	Insomnia, depression
Renal and Urinary Disorders	Renal tubular necrosis, renal impairment, dysuria, hematuria, hydronephrosis, bladder spasm, urinary retention	—
Respiratory, Thoracic and Mediastinal Disorders	Cough, dyspnea, dyspnea exertional	Cough, dyspnea, pharyngolaryngeal pain, sinus congestion
Skin and Subcutaneous Tissue Disorders	Acne, pruritus	Rash, contusion
Surgical and Medical Procedures	Complications of transplant surgery, postoperative complications, postoperative wound complication	—
Vascular Disorders	Hypertension, hypertension aggravated, hypotension	Hypertension

*USP (MODIFIED)



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

Practice Pointers

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 Montréal, 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 youth 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 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 neuro-cognitive 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.
- 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. ●

For adult providers

The process of transition to adult care doesn't end at the time of transfer.

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KIDNEY WEEK

CAREER FAIR

November 1st, 2nd & 3rd, 2012

9:30 AM – 2:30 PM

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San Diego, California

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!