Managing Anemia in Patients With Chronic Kidney Disease

Chronic kidney disease (CKD), which is increasing in prevalence, results in significant morbidity, mortality, and health care costs in the United States. According to data collected from the National Health and Nutrition Examination Survey (1999 to 2004), 11.5% of adults (more women than men) have evidence of CKD. These estimates rise in patients with diabetes and hypertension, with more than 35% of adults with diabetes and more than 20% of those with hypertension suffering from CKD.

According to the National Kidney Foundation (NKF), the presence of kidney disease should be established and assigned a level according to the NKF Kidney Disease Outcomes Quality Initiative (KDOQI) classification, which is summarized in Table 1. Diagnosis is established by the presence of structural or functional abnormalities with or without decreased glomerular filtration rate (GFR) or a GFR less than 60 mL per minute per 1.73 m² with or without kidney damage, for a period of at least 3 months.

Causes and Consequences Of Anemia and Iron Deficiency

Anemia, defined in the KDOQI guidelines as a hemoglobin less than 13.5 g/dL in adult men and less than 12 g/dL in adult women, is a common complication of...
CKD. Its prevalence increases with increasing stage of CKD, such that nearly all patients with stage 5 CKD are affected. Patients with CKD may have absolute iron deficiency, which occurs when erythropoiesis increases due to ESA use. Ferritin concentration and transferrin saturation are indices commonly used to evaluate iron stores and assess for iron-deficiency anemia. Ferritin is an indirect measure of iron stores, whereas transferrin is the carrier protein for iron. In the KDOQI guidelines, the goal serum ferritin level is greater than 100 ng/mL (>200 ng/mL in patients undergoing dialysis), and the target transferrin saturation is greater than 20%. Patients with CKD frequently experience iron deficiency, especially those with end-stage renal disease (ESRD) who are receiving hemodialysis. Hemodialysis results in losses of 6 to 7 mg of iron per day of dialysis, which is compounded by physiologic losses and loss from periodic venipuncture. It is estimated that patients receiving hemodialysis can have annual iron losses that exceed 1.5 to 3 g, which exceeds total body stores.

Iron Therapy

Iron is available in oral or parenteral dosage forms. Oral iron is relatively inexpensive and easy to administer; however, there are some limitations to its use. Gastrointestinal (GI) adverse events (AEs) such as constipation, dyspepsia, bloating, nausea, diarrhea, and heartburn may affect up to 20% of patients. These GI effects can be minimized if iron supplements are taken with food, but the presence of food will decrease iron absorption. Other factors that can decrease absorption are the use of phosphate binders or acid suppressive therapy, as well as the presence of hepcidin (produced by the liver during inflammation). Frequent dosing requirements (often 3 times per day) that can result in poor adherence also can limit the use of oral iron. Furthermore, the use of ESAs can increase the demand for iron beyond the amount that can be given orally.

Rozen-Zvi et al conducted a systematic review and meta-analysis to compare IV and oral iron supplementation for the treatment of anemia in patients with stage 3 to 5 CKD. Thirteen randomized controlled trials comparing oral iron with IV iron were included in the analysis. The primary outcome of interest was the absolute hemoglobin level or change in hemoglobin from baseline after 2 to 3 months of therapy. There were a variety of secondary outcomes including all-cause mortality, cardiovascular morbidity and mortality, bacterial infections, need for renal replacement therapy, iron indices, ESA dose, hospitalizations, QoL, and need for transfusion. Efficacy analyses were conducted separately for patients who were receiving dialysis and those who were not.

The results revealed that the hemoglobin level was significantly increased among patients on dialysis (n=7 trials) who received IV iron therapy compared with those who received oral iron therapy (weighted mean

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR (mL/min/1.73 m²)</th>
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<tbody>
<tr>
<td>1</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
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<tr>
<td>3</td>
<td>30-59</td>
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<tr>
<td>4</td>
<td>15-29</td>
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<tr>
<td>5</td>
<td>&lt;15 or receiving dialysis</td>
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CKD, chronic kidney disease; GFR, glomerular filtration rate; KDOQI, Kidney Disease Outcomes Quality Initiative

Based on reference 1.

Table 1. KDOQI Classification Of CKD
difference [WMD], 0.83 mg/dL; 95% confidence interval [CI], 0.09-1.57). Furthermore, the ESA dose decreased significantly (WMD, –28.21 units/kg per week; 95% CI, –42.12 to –14.3) and ferritin levels significantly increased (WMD, 172.34 ng/mL; 95% CI, 111.31-233.38) in patients treated with IV iron. No changes were found with regard to transferrin saturation, and data were not available for QoL. In patients with CKD not receiving dialysis, a small increase in hemoglobin associated with IV iron therapy was noted (WMD, 0.31 g/dL; 95% CI, 0.09-0.53); however, the authors judged this change to be clinically unimportant. Ferritin levels (WMD, 213.35 ng/mL; 95% CI, 56.5-370.2) and transferrin saturation (WMD, 9.45%; 95% CI, 1.9%-17.1%) were significantly increased in the IV iron group. QoL was reported in a single trial, and IV iron was associated with an improvement among patients not receiving dialysis.

Safety was reported for the combined population, and there were no differences in all-cause mortality, serious AEs, or need for transfusion between the oral and IV iron therapy groups. Hospitalization rate was reported in a single paper, with no differences found between groups. No data were available for cardiovascular morbidity and mortality and bacterial infections. There was no difference in the need for renal replacement therapy among patients who were not receiving dialysis initially. The authors concluded that IV iron therapy was more effective than oral iron therapy for improving hemoglobin levels in patients receiving dialysis, but they noted that the effect among those not receiving dialysis was small and clinically unimportant.

Either oral or IV iron therapy may be used for initial management of patients not receiving dialysis and those receiving peritoneal dialysis, but IV iron therapy is recommended strongly for patients undergoing hemodialysis. The KDOQI guidelines do not recommend any particular preparation of IV iron, and these products generally are considered equivalent on a milligram-per-milligram basis (Table 2). Although iron dextran regimens have been administered safely, it is important to consider that with the information available today on the safety profile of sodium ferric gluconate and iron sucrose, many clinicians would consider these newer agents as first-line therapy.

**ESA Therapy**

Epoetin alfa (Epogen, Amgen; Procrit, Janssen) and darbepoetin alfa (Aranesp, Amgen) are effective in

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Usual Adult Dose</th>
<th>Administration</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Iron dextran (Infed, Waton; Dextrum, American Regent)</td>
<td>Total dose (mL)=0.0442 x (desired hemoglobin – observed hemoglobin) x lean body weight (kg) + (0.26 x lean body weight); small doses (such as 50-100 mg), given regularly until response</td>
<td>Given undiluted by slow IV injection (≤50 mg/min)</td>
<td>• Due to the potential for anaphylaxis, a test dose is required prior to the first therapeutic dose. • Resuscitative medication and personnel should be available each time iron dextran is administered.</td>
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<tr>
<td>Sodium ferric gluconate (Ferrlecit, Sanofi-aventis; Nulecit, Watson)</td>
<td>Hemodialysis recipients: 125 mg IV (expressed as elemental iron); most patients will require a minimum dose of 1,000 mg elemental iron over 8 dialysis sessions</td>
<td>May be diluted and given by slow IV infusion over 1 h or given undiluted by slow IV injection at a rate up to 12.5 mg/min at end of dialysis</td>
<td>• Has been associated with hypotension and flushing; reducing the dose and infusing the drug over 4 h has been shown to reduce these effects.</td>
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<tr>
<td>Iron sucrose (Venofer, American Regent)</td>
<td>Hemodialysis recipients: 100 mg at each consecutive dialysis session for a total cumulative dose of 1,000 mg Non-dialysis chronic kidney disease: 200 mg on 5 different occasions within 14 d</td>
<td>Given undiluted by slow IV injection at a rate ≤20 mg/min (over 2-5 min); may also be given by IV infusion directly into the dialysis line over ≥15 min after dilution in normal saline.</td>
<td>Slow injection is necessary to reduce the risk for hypotension.</td>
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<tr>
<td>Ferumoxytol (Feraheme, Amag)</td>
<td>510 mg IV x 1 dose, followed by 510 mg IV 3-8 d later</td>
<td>Given undiluted at a rate ≤1 mL (30 mg)/sec</td>
<td>• Regimen may be repeated after 1 mo if needed. • This preparation is relatively well tolerated and may be given rapidly. • There are no published comparative studies with other IV iron preparations.</td>
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**Table 2. Summary of IV Iron Preparations**

ESAs, erythropoiesis-stimulating agents

Based on references 4, 10, and 12-14.
raising hemoglobin, but their use has come under increased scrutiny in recent years. In March 2007, the FDA required that a boxed warning be added to the ESA product labels and that updates be made in the “warnings” and “dosage and administration” sections. In June 2011, the FDA again recommended updating of the label; these changes are summarized in Table 3.

In addition to the labeling changes, as of February 2010, ESAs also are prescribed under a risk evaluation and mitigation strategy (REMS). Components of the REMS include a medication guide for all patients (approved in 2008) and a prescribing program for patients receiving the drugs for cancer-associated anemia.

The ESA labeling changes specific for CKD were based largely on results from 2 trials published in 2006—CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) and CREATE (Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta). The CHOIR trial, patients with CKD not receiving dialysis were randomized to epoetin alfa to achieve a target hemoglobin of 13.5 g/dL (n=715) or 11.3 g/dL (n=717). The primary end point was the time to the composite of death or myocardial infarction (MI), hospitalization for congestive heart failure (CHF), or stroke. The data and safety monitoring board stopped the trial early when they realized that it was unlikely that the high-hemoglobin group was going to show a benefit. The median study duration was 16 months. The primary end point occurred in more patients in the high-hemoglobin group (125 vs 97; hazard ratio [HR], 1.34; 95% CI, 1.03-1.74; P=0.03). The results were driven by a higher incidence of death and CHF hospitalization in the high-hemoglobin group. No differences were found in QoL between groups, and more patients in the high-hemoglobin group reported at least 1 AE (376 of 686 [54.8%] vs 334 of 688 [48.5%]; P=0.02). The authors concluded that a target hemoglobin of 13.5 g/dL was associated with greater risk for harm and no improvements in QoL compared with a target of 11.3 g/dL. A secondary analysis of data from CHOIR found that significantly more patients randomized to the high-hemoglobin group were unable to achieve target hemoglobin concentrations and required high doses of epoetin alfa. Patients who were able to achieve hemoglobin targets (in both groups) had better outcomes than those who could not. Furthermore, no increased risk was found with high-hemoglobin targets in patients who achieved their randomized target.

The CREATE trial randomized patients with CKD (GFR, 15-35 mL/min per 1.73 m²) to epoetin beta (not available in the United States) to target hemoglobin levels of 13 to 15 g/dL (n=301) or 10.5 to 11.5 g/dL (n=302). The primary end point was time to first cardiovascular event (composite of sudden death, MI, acute heart failure, stroke, transient ischemic attack, angina resulting in hospitalization, complication of peripheral vascular disease, or arrhythmia requiring hospitalization). There was no significant difference between groups in incidence of the primary end point (HR, 0.78; 95% CI, 0.53-1.14; P=0.20). QoL improved significantly with target hemoglobin levels of 13 to 15 g/dL. Overall, there were no significant differences in AEs between groups, but the incidences of headache and hypertensive episodes were higher in the 13- to 15-g/dL group. The authors concluded that complete correction of hemoglobin level did not lead to a reduction in the risk for cardiac events.

A third pivotal trial was published after the ESA labeling changes. TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) differed from CHOIR and CREATE in that it was a randomized, double-blind, placebo-controlled trial. Patients with CKD and type 2 diabetes were randomized to darbepoetin alfa to achieve a hemoglobin level of 13 g/dL (n=2,012), or placebo (n=2,026) with rescue darbepoetin alfa if the hemoglobin fell below 9 g/dL. The primary end points were the composite of death or a cardiovascular event (nonfatal MI, CHF, stroke, or hospitalization for myocardial ischemia) or the composite of time to death or ESRD. There were no significant differences between groups in terms of death or a cardiovascular event (HR, 1.05; 95% CI, 0.95-1.17; P=0.41) or for death or ESRD (HR, 1.06; 95% CI, 0.95-1.19; P=0.29). Fatal or nonfatal stroke occurred in almost twice as many patients assigned to darbepoetin (101 vs 53; HR, 1.92; 95% CI, 1.38-2.68; P<0.001). Transfusions were significantly more common in placebo recipients (496 vs 297; P<0.001). No clinically important differences in QoL were reported between the groups. The authors concluded that the use of darbepoetin in patients with type 2 diabetes and CKD was not associated with improvements in the primary
end point of death or cardiovascular events, or death or development of ESRD. However, they pointed out that such therapy was associated with an increased incidence of stroke, and they concluded the risk associated with therapy outweighed potential benefits for many patients.

Results from CHOIR, CREATE, and TREAT reveal that ESA therapy may be associated with harm in patients with CKD, and that targeting high-hemoglobin levels does not appear to be beneficial. Unanswered questions remain, however, with respect to a precise hemoglobin target and optimal dosing of ESAs.

The KDOQI guidelines have not been updated to reflect information in the TREAT trial; however, the CHOIR and CREATE papers were among those considered when the hemoglobin target was reduced to 11 to 12 g/dL.8 Therefore, there is still a place in therapy for ESAs to treat anemia in patients with CKD. Subcutaneous therapy is recommended for patients who are not receiving dialysis, whereas IV therapy is suggested for those receiving hemodialysis, based on convenience of administration.8 Frequency of administration and dose are left to the discretion of the prescriber and should be based on the clinical condition of the patient. Red blood cell transfusions are an option for the treatment of anemia in patients with CKD; however, their use should be judicious because patients may develop antibodies that may affect a kidney transplant. There is no defined hemoglobin level at which transfusion is recommended.

Peginesatide (OMONTYS, Affymax/Takeda), a new ESA, was approved by the FDA in March 2012 for anemia in patients receiving dialysis.22,23 Although peginesatide stimulates the erythropoietin receptor, it is not structurally similar to erythropoietin.24 Two clinical trials (EMERALD 1 and 2) support the noninferiority of peginesatide to epoetin alfa or beta; however, complete publication of these trials is lacking at this time.23,24 One advantage of peginesatide is its once-monthly dosage regimen; the initial dose is 0.04 mg/kg IV or subcutaneously once monthly. Detailed dosage recommendations for converting patients from epoetin or darbepoetin are provided in the package labeling.23 Initial data indicate that peginesatide has reasonable efficacy and safety; however, post-marketing studies evaluating cardiovascular safety have been required by the FDA.25,26 The 2 clinical trials evaluating peginesatide for anemia in non-dialysis CKD patients (PEARL 1 and 2) found an increased risk for cardiovascular events; thus, peginesatide should not be used for patients who are not receiving dialysis.24

### Medication Management In Patients With CKD

Dialysis patients take an average of 11 medications, and are believed to have the highest pill burden of all chronically ill patients.27 The use of a large number of medications can result in reduced adherence to the medication regimen and decreased QoL.27-29 In addition to a high pill burden, drug-related problems occur in dialysis patients at a high rate. A 2005 study found a rate of 4 drug-related problems per dialysis patient.30,31 Improvements in patient education and continuity of care may help reduce drug-related problems in dialysis or CKD patients.

Pai and colleagues randomized 104 hemodialysis patients to in-depth pharmaceutical care or usual care over the course of 2 years.32 Patients receiving pharmaceutical care underwent a program of drug therapy review that included patient education, health care provider education, and compilation of a drug profile, as well as a review of the medical and laboratory records with a pharmacist every 8 weeks. At the end of the study period, patients in the pharmaceutical care group had fewer hospitalizations and a 14% reduction in the number of medications they used. The investigators identified and resolved 530 drug-related problems in this group. This study suggests that detailed patient education and proactive pharmacist intervention not only reduces the pill burden in dialysis patients but also promotes appropriate medication use and improves medical outcomes.

The continuity of care for patients with CKD often is interrupted by hospitalization. Hospitalized CKD patients have alterations in anemia management and decreased hemoglobin levels.33 Other drug-related

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**Table 3. Summary of ESA Labeling Changes**

<table>
<thead>
<tr>
<th>Section</th>
<th>Key Label Information Related to CKD</th>
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<tr>
<td><strong>Boxed warning</strong></td>
<td>• ESAs increase the risk for death, serious cardiac events, and stroke when the target hemoglobin is &gt;11 g/dL. • No trial has determined an ESA dose or target hemoglobin level that does not increase risk. • Use the lowest ESA dose to avoid the need for RBC transfusions.</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>• Monitor hemoglobin levels at least weekly until stable. • Consider initiating ESAs when the hemoglobin is &lt;10 g/dL. • Use patient-specific dosing with the lowest dose possible to avoid RBC transfusions.</td>
</tr>
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CKD, chronic kidney disease; ESAs, erythropoiesis-stimulating agents; RBC, red blood cell.

Based on reference 16.
complications also can occur due to problems with continuity of care. In fact, Ong and colleagues found that 65% of drug-related problems in patients with CKD were the result of incomplete medical information transfer between health care settings. Thus, improved medication reconciliation during care transitions has the potential to dramatically reduce drug-related problems in patients with CKD. St. Peter recently developed recommendations for the dialysis medication reconciliation team. Within 12 to 24 hours of admission the inpatient team should be provided with a list of current medications, discontinued medications, drug allergies, and adverse reactions, as well as any other relevant information. At discharge, the dialysis medication reconciliation team should be responsible for obtaining the list of discharge medications. The list must be reviewed in detail for discontinued medications, dosage changes, or new medications; the rationale for any medication changes should be documented.

**Conclusion**

Appropriate management of anemia in patients with CKD requires iron supplementation and ESA therapy. IV iron therapy is recommended for patients receiving hemodialysis; however, oral iron supplementation may be appropriate for non-dialysis patients or those receiving peritoneal dialysis. The KDOQI guidelines suggest a target hemoglobin level of 11 to 12 g/dL in patients receiving ESA therapy; however, package labels for ESA agents no longer recommend a target hemoglobin range for ESA therapy.

Medication management for patients with CKD-associated anemia is an important role for pharmacists. Patients with CKD often have complicated medication regimens and frequent hospitalizations, making patient education and medication reconciliation key components of successful pharmacotherapy.

**References**


Reports from the PBMI conference

Cost Containment
In Specialty Pharmacy

Scottsdale, Ariz.—Specialty pharmacy medications represent a significant source of pharmacy costs for most employers trying to keep their pharmacy benefits in check. Although they make up fewer than 20% of overall prescriptions today, according to Medco Health Solutions’ 2011 trend report, specialty drug spending saw a 22% increase in its total market share between 2009 and 2010 and further growth is predicted for the coming decade. The nonprofit accrediting body URAC has predicted that specialty drugs will make up the majority of new drug approvals in coming years and will account for approximately 40% of a health plan’s drug spending by 2020.

With numbers like these, it’s little wonder that pharmacy benefits are emphasizing cost containment initiatives. Such initiatives were key topics in many of the presentations at the Pharmacy Benefit Management Institute’s 2012 Drug Benefit Conference in February.

For example, Walgreens has a number of cost containment strategies for its specialty pharmacy program, such as compliance management, divided dispensing and site of care optimization (related article, page 11). Aggressive management of patient compliance/adherence is one such initiative, Michael Einodshofer, director of utilization management for Walgreens Specialty Pharmacy told Specialty Pharmacy Continuum. In addition to influencing patient outcomes (Table, page 11), compliance can have a huge affect on cost. Mr. Einodshofer noted that Walgreens has preliminary results showing that a compliant patient can reduce pharmacy costs for most employers trying to keep their pharmacy benefits in check.

Excelera Eyes Market Growth For Hospitals

Several health systems have made the foray into the specialty pharmacy market. But with their limited scale and lack of national exposure, it is difficult for them to convince manufacturers and insurers that they can supply medications and patient management programs at a reduced cost, and also deliver the utilization and outcomes data that pharmacy needs for research and marketing.

Now some health systems are tackling this size challenge. A group led by Parvice Health System at Minnesota and Henry Ford Health System in Michigan has established a national network of hospital pharmacies called ExceleraRx, LLC.

Breadth of problem is ‘scary’
Do MTX Drug Interactions Fall Below Radar?

A dangerous interaction between proton pump inhibitors (PPIs) and methotrexate that prompted the FDA to issue a warning late last year represents just the tip of the iceberg of potentially serious interactions that can occur when common medications are given concomitantly with methotrexate.

“It’s pretty scary how many of these interactions there are,” said Ali McBride, PharmD, clinical pharmacy specialist at the Alvin J. Siteman Cancer Center at Barnes-Jewish Hospital in St. Louis.