Kidney Learning System™

NATIONAL KIDNEY FOUNDATION

presents:

Anemia:

Mobilizing Resources for Positive Outcomes

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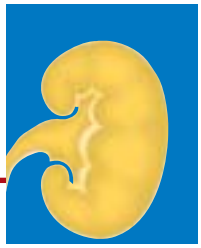
This learning activity was made possible by an educational grant from Ortho Biotech Products, L.P.



Target Audience

This activity is designed for nephrologists and other health care professionals who are involved with the care and treatment of patients with chronic kidney disease (CKD).

Statement of Need

In the U.S. alone, 20 million adults have CKD and another 20 million are at increased risk for developing CKD. Most people with CKD develop anemia due to insufficient production of erythropoietin (EPO) by the diseased kidneys. When untreated, anemia of CKD is associated with a number of physiological abnormalities including decreased oxygen delivery and utilization, increased cardiac output, congestive heart failure, decreased cognitive ability and impaired immune responsiveness. These abnormalities reduce quality of life, compromise opportunities for rehabilitation and decrease patient survival. Clinicians must recognize their role in the effective treatment of the anemia of CKD so they can improve survival, decrease morbidity and improve the quality of life of their patients. Overall outcomes of CKD patients could be improved significantly by the appropriate evaluation and management of anemia. There is a growing need for awareness and understanding of issues related to anemia management in CKD by health care providers to improve patient outcomes on an ongoing basis.

Overall Program Goal

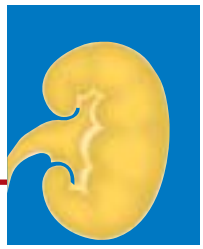
The purpose of this educational activity is to identify strategies for anemia therapy that can be used by the multidisciplinary care team to optimize anemia management in CKD, such as extended dosing schedules.

Learning Objectives

Upon completion of this activity, participants will be able to:

- Discuss the use of the K/DOQI guidelines for the stratification and management of patients with CKD
- Describe the prevalence of CKD as well as the prevalence of anemia associated with CKD
- Describe collaborative approaches to the management of anemia in CKD patients
- Discuss the application of new clinical approaches to optimize anemia management in these patients

Anemia:
Mobilizing Resources for Positive Outcomes



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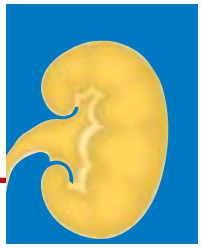
CME and CE Information

Physician Accreditation

The National Kidney Foundation (NKF) is accredited by the Accreditation Council of Continuing Medical Education to provide continuing medical education for physicians. The NKF designates this educational activity for a maximum of 2.0 hours in Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the activity.

Nursing Accreditation

This continuing nursing education activity was approved by the New York State Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.



Dietitian Accreditation

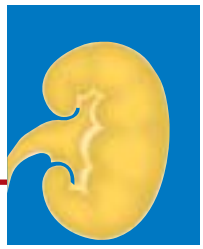
A maximum of 2.0 continuing professional education (CPE) credits for registered dietitians have been approved through the Commission on Dietetic Registration of the American Dietetic Association.

Disclaimer

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) *Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification* (published in February 2002) are based on the best information available at the time of publication. They are designed to provide information and assist in decision-making. They are not intended to define a standard of care and should not be construed as doing so, nor should they be interpreted as prescribing an exclusive course of management.

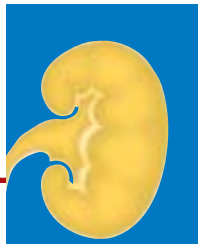
Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources and limitations unique to an institution or type of practice. Every health care professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

The views presented herein are those of the faculty and not necessarily those of the National Kidney Foundation or Ortho Biotech Products, L.P. This material is prepared based on a review of multiple sources of information, but is not exhaustive of the subject matter. Therefore, health care professionals and other individuals should review and consider other publications and materials about the subject matter before relying solely on the information contained within this material.



Acronyms and Abbreviations

CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
CHOIR	Correction of Hemoglobin and Outcomes in Renal Insufficiency
C_{Cr}	Creatinine Clearance
ESRD	End Stage Renal Disease
EPO	Erythropoietin
GFR	Glomerular Filtration Rate
HRQOL	Health-Related Quality of Life
Hb	Hemoglobin
K/DOQI	Kidney Disease Outcomes Quality Initiative
KDQ	Kidney Disease Questionnaire
KEEP	Kidney Early Evaluation Program
LV	Left Ventricular
LVH	Left Ventricular Hypertrophy
LASA	Linear Analog Scale Assessment
MDRDS	Modification of Diet in Renal Disease Study
NHANES III	Third National Health and Nutrition Examination Survey
NIDDK	The National Institute of Diabetes & Digestive & Kidney Diseases
NKDEP	National Kidney Disease Education Program
NKF	National Kidney Foundation
PAERI	Prevalence of Anemia in Early Renal Insufficiency
PROMPT	Procrit® for Maintenance Phase Treatment Trial
QOL	Quality of Life
RPA	Renal Physicians Association
RRT	Renal Replacement Therapy
RAPID	Retrospective Review of Alternate Procrit® Dosing Trial
S_{Cr}	Serum Creatinine



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Applying the Common Language of K/DOQI

"K/DOQI is trying to get us on the same page in terms of identifying patients with CKD and using standard approaches to delay or halt its progression and prevent complications..." *— Paul L. Kimmel, MD*

The Tip of the Iceberg

Patients with Stage 5 chronic kidney disease (formerly called end stage renal disease, or ESRD) represent only the tip of the iceberg in terms of the number of patients with chronic kidney disease (CKD).[1] More than 20 million Americans have CKD and another 20 million are at increased risk for developing CKD. More than 300,000 individuals have stage 5 CKD and are at the tip of the iceberg. However, most patients with CKD are at the bottom of the iceberg, below sea level, ranging from Stages 1 to 3 in the National Kidney Foundation's (NKF) Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines for the evaluation, classification and stratification of CKD.

K/DOQI defines and classifies CKD into 5 stages based on glomerular filtration rate (GFR) and presence or absence of kidney damage, with recommended action steps for each clinical stage.[1] (See Table 1.) K/DOQI attempts to standardize CKD identification and develop uniform approaches to delay or halt its progression and prevent complications.

In Stages 1 and 2, CKD should be diagnosed and a treatment plan initiated, which includes treating comorbid conditions, attempting to slow progression of kidney disease, and beginning to reduce the risk of car-

Table 1

Stages of CKD and Recommended Clinical Action

Stage	Description	GFR (mL/min/1.73 m²)	Action*
1	Kidney damage with normal or ↑ GFR	≥ 90	Diagnosis and treatment Treatment of comorbid conditions Slowing progression CVD risk reduction
2	Kidney damage with mild ↓ GFR	60–89†	Estimating progression
3	Moderate ↓ GFR	30–59	Evaluating and treating complications
4	Severe ↓ GFR	15–29	Preparation for kidney replacement therapy
5	Kidney failure	< 15 or dialysis	Replacement, if uremia present

CVD, cardiovascular disease
*Includes actions from preceding stages.
†May be normal in infants and the elderly.

Adapted with permission from the National Kidney Foundation. Am J Kidney Dis. 2002;39(2 suppl 1):S25.

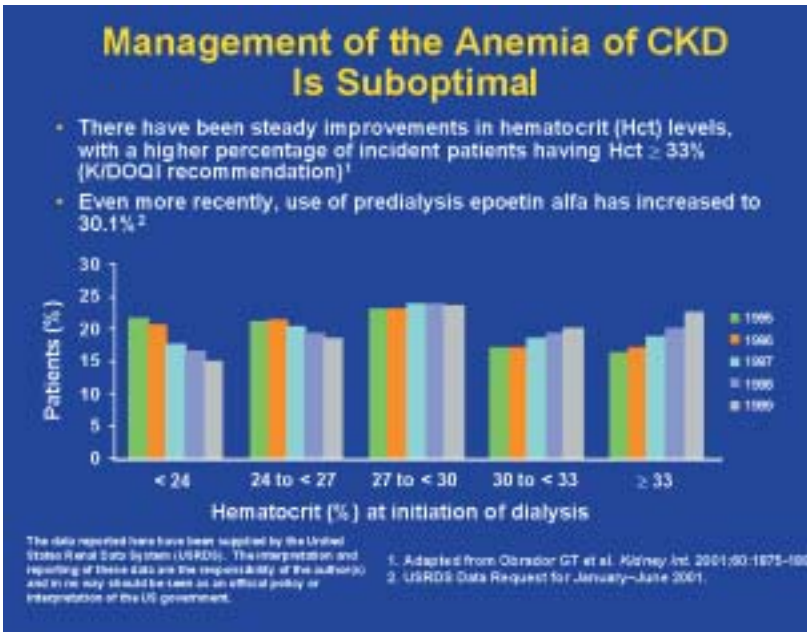
diovascular disease (CVD). For Stage 3, clinicians should continue to estimate the rates of disease progression and follow the treatment plan set forth in Stages 1 and 2. Additionally, the guidelines recommend beginning to evaluate and treat developing complications in Stage 3. In Stages 4 and 5, clinicians should start to prepare patients for renal replacement therapy (RRT) and initiate RRT when GFR is <15 mL/min/1.73 m^2 or when uremia is present.

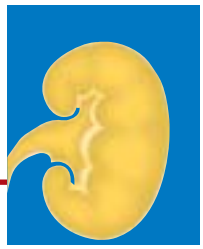
In a similar vein, Clinical Practice Guideline Number 3 from the Renal Physicians Association (RPA), "Appropriate Patient Preparation for Renal Replacement Therapy," is aligned with the K/DOQI guidelines but focuses on patients with Stages 4 and 5 CKD.[2] The RPA's guidelines, like the K/DOQI's, focus on slowing the progression of kidney disease and identifying and managing comorbidities.

Common Comorbidities in CKD

In a retrospective claims analysis of predialysis patients, hypertension and diabetes were extremely common, as expected, and a substantial number of patients had anemia and CVD.[3] The scope of anemia in CKD has been characterized in separate analyses using data from the Third National Health and Nutrition Examination Survey (NHANES III). Using the Cockcroft-Gault equation to estimate kidney function (Hsu et al), more than 13 million American adults are believed to have creatinine clearance (C_{Cr}) levels ≤ 50 mL/min, and 12% of these individuals have hemoglobin levels < 12 g/dL.[4] In another analysis, using the formula from the Modification of Diet in Renal Disease Study (MDRDS) to calculate GFR (mL/min/1.73 m^2), a slightly different kidney function boundary was used (GFR < 60 mL/min/1.73 m^2). The prevalence of anemia

Figure 1





reflected the same pattern of increasing prevalence with decreasing GFR. At the earlier stages of CKD, the prevalence of anemia is approximately 1% to 2%; it increases to about 5% in Stage 3 patients and to almost 50% of the patients during Stage 4.[5]

Although the percentage of anemic patients has decreased over time, a significant number of patients still have anemia.[6] (See Figure 1.)

CKD Programs and Guidelines

"Only 10% of 1,936 incident dialysis patients were receiving epoetin alfa. Only 20% had vascular access created in the year before they started dialysis. The numbers for treatment with iron and vitamin D are dismal, and interestingly enough, only one third of those patients in an HMO were sent to nephrologists." *— Paul L. Kimmel, MD, quoting from London et al.*[3] (See Table 2.)

The public health implications of such large cohorts of patients have drawn the attention of public policy makers. Many programs have been developed to improve the care of patients with CKD.

1. A chapter on CKD was included in Healthy People 2010, the roadmap of the Surgeon General's office for addressing public health problems in the United States.[7]
2. The K/DOQI and RPA clinical practice guidelines provide a framework for health care professionals involved in the management of patients across the continuum of CKD.[1,2]
3. The National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) is spearheading the National Kidney Disease Education Program (NKDEP), which is aimed at patients with CKD and general medical practitioners.

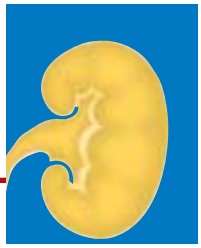
Table 2

Management of the Anemia of CKD Is Suboptimal (cont)

Expected intervention	Total no. receiving expected intervention (%)
Epoetin alfa use	203 (10.5)
Vascular access	403 (20.8)
Iron	131 (6.8)
Vitamin D	78 (4.0)
PO_4 binders	149 (7.7)
Nephrology visits	576 (29.8)

N = 1,936.

Adapted with permission from London R et al. Am J Kidney Dis. 2002;40:638-648.



4. The NKF's Kidney Early Evaluation Program (KEEP) is a community-based initiative for early identification of individuals at increased risk for CKD. More than 25,000 Americans have already participated in this kidney health screening. (Ortho Biotech Products, L.P. is the primary sponsor of KEEP.)

Such efforts are extremely important, considering the current suboptimal management of CKD and the increasing number of potential CKD patients.

A retrospective claims analysis of almost 2,000 patients showed that in the year before dialysis, only 10% received epoetin alfa, 20% had a vascular access created, and one third visited a nephrologist.[3] In a prospective cohort study involving more than 800 patients at 81 U.S. dialysis facilities, only half the patients had their first nephrology visit in the year before dialysis.[8] Earlier referral and frequent visits to a nephrologist have been associated with lower morbidity and mortality.[9,10]

Key Points

Early recognition and management of CKD and its major comorbidities and complications, such as anemia and CVD, are expected to produce better outcomes and delay disease progression. K/DOQI provides the medical community with guidelines regarding the care of patients with CKD, as well as a platform for categorizing and reporting results.

Anemia of CKD: A Model for Collaborative Care

"Over 50% of patients with CKD have some form of cardiovascular disease, ranging from congestive heart failure to left ventricular hypertrophy." — *Ajay K. Singh, MD, MRCP, MBA, quoting from the Prevalence of Anemia in Early Renal Insufficiency (PAERI) study (presented at the 2002 Meeting of the American Society of Nephrology)*

The Link Between Anemia, Cardiovascular Disease and CKD

Multiple comorbidities complicate the management of patients with CKD, particularly anemia and CVD. Final results from the Prevalence of Anemia in Early Renal Insufficiency (PAERI) study were presented at the 2002 Meeting of the American Society of Nephrology.[11-13] In this prospective, multicenter U.S. study, 5,222 patients at more than 230 practices were evaluated. The definition of CKD was a serum creatinine (S_{Cr}) level of 1.5 to 6.0 mg/dL. Approximately half the patients had CVD, which emphasizes the connection between CKD and CVD. Additionally, nearly half the patients had anemia (hemoglobin level ≤ 12 g/dL).

The link between CKD and CVD is important to recognize. Left ventricular hypertrophy (LVH) begins early in CKD, affecting approximately one quarter of patients with C_{Cr} levels > 50 mL/min and worsening as the disease progresses.[14] A hemoglobin decrease of 0.5 g/dL increases the risk of left ventricular growth by 32%;[15] a decrease of 1 g/dL is associated with a 6% increase in the risk of LVH.[15] (See Table 3.)

Table 3

Factors Associated With Left Ventricular Hypertrophy (LVH)

Risk factor	Change	Increase in risk of LVH	p value
Decrease in creatinine clearance	5 mL/min	3%	0.0168
Decrease in Hb level	1 g/dL	6%	0.0062
Increase in systolic blood pressure	5 mm Hg	3%	0.0018

N = 176 patients followed from 2/1990 to 3/1993.

Levin A et al. Am J Kidney Dis. 1996;27:347-354.

These cardiovascular changes begin long before patients require dialysis.[14] It is important to recognize the strong relationship between heart damage in patients with CKD and their decreased survival rate.[16] Consequently, researchers have questioned whether anemia correction could improve CVD status, and some studies have shown positive results.[17,18] The treatment of anemia has been shown to decrease LV mass index, which suggests that LVH is reversible.[17] (See Figure 2.)

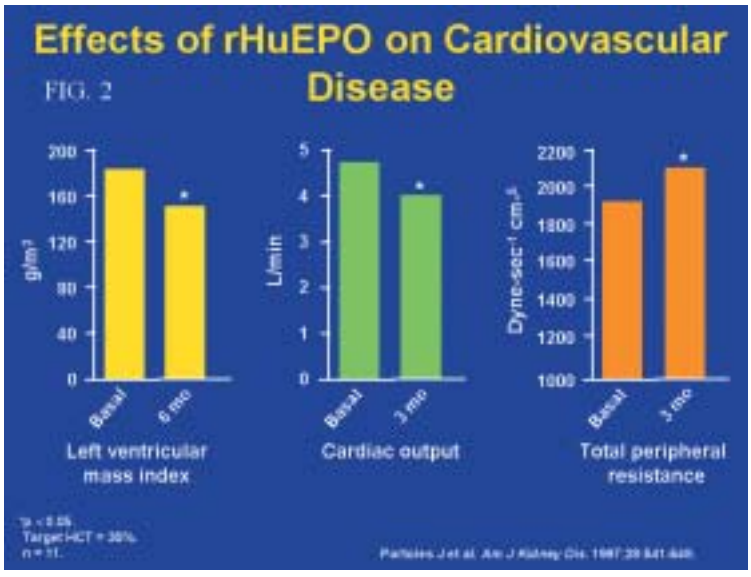
The greater the level of anemia correction, the greater the improvement in LV mass index.[18] The time to manage anemia is during the earlier stages of CKD, long before dialysis is required.[19] In addition, clinical evidence suggests that anemia correction can significantly delay the progression of CVD in CKD.[20]

The Importance of Early Referral to Nephrology

The nephrologist's ability to manage anemia and CVD adequately is compromised by late referral. Although different boundaries have been used in studies to differentiate "early" and "late" referral, earlier referral and more frequent nephrologist visits are associated with a decreased risk of death compared with later referral and fewer visits.[9,10] Consequences of late referral can include increased morbidity and mortality and lack of a permanent vascular access.[21] Late referral is also associated with lower hemoglobin levels and less pre-ESRD epoetin alfa use; 3 times as many patients referred early have been treated with epoetin alfa.[10] (see Table 4.)

Patients who receive more consistent epoetin alfa treatment have higher hematocrit

Figure 2



levels at the start of ESRD and improved survival one year after ESRD diagnosis.[22] Thus, early referral presents the opportunity for important interventions and a potentially better outcome.[23] However, the number of nephrologists is clearly insufficient to treat the increasing number of CKD patients.

Collaborative Care Is Critical

A collaborative approach to patient care will lead to improved outcomes in CKD. With the large number of CKD patients and limited number of nephrologists, multidisciplinary care becomes critical in the management of CKD.

Outreach to primary care physicians, nurse practitioners, social workers, and dietitians is necessary to reduce and adequately manage the number of people who develop CKD and progress to Stage 5.[25] Multidisciplinary predialysis care has been associated with significantly fewer urgent dialysis starts, fewer days in the hospital in the first month of dialysis, more outpatient education, and substantial cost savings.[24] Essential elements for success include early referral and adequate resources for a dedicated CKD staff.[24]

"Given the size of the population with CKD, the lack of nephrologists in the next 5 to 10 years and the gap that creates…a lot of this care is going to happen in the internal medicine/family practice arena."*—Ajay K. Singh, MD, MRCP, MBA*

Key Points

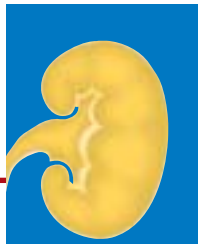
CKD is associated with a spectrum of comorbidities, but outcomes can be improved. Anemia is prevalent in CKD and is an important risk factor for CVD. Early management of anemia with epoetin alfa leads to improved outcomes. To achieve positive outcomes, a multidisciplinary or collaborative approach is of paramount importance.

Table 4

Association of Laboratory Parameters and Pre-ESRD Epoetin Alfa Use With Timing of Nephrology Referral*

	Study Population	Late referral	Early referral
Laboratory parameters			
Hemoglobin (g/dL)	10.1 ± 1.8	9.9 ± 1.9	10.2 ± 1.8†
Hematocrit (%)	30.4 ± 6.0	29.8 ± 6.2	30.7 ± 5.8‡
% of pre-ESRD epoetin alfa use	25.2	10.5	32.0†

*[illegible] versus > 4 months before ESRD start.
†p < 0.001 for bivariate comparisons.
‡p < 0.01 for bivariate comparisons.
Black AG. Am J Kidney Dis. 2003;41:S10-S16.



Anemia Management: Achieving Control With Extended Dosing Regimens

The Emergence of Extended Dosing Schedules for Erythropoietic Agents

Two therapies are currently available in the United States for the treatment of anemia in patients with CKD: epoetin alfa and darbepoetin alfa.

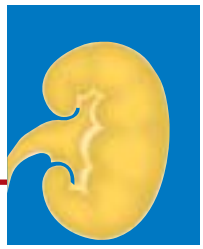
1. Epoetin alfa indications:
   a. Patients with chronic kidney failure (approved in 1989)
   b. Patients with cancer on chemotherapy (approved in 1993)
   c. Zidovudine-treated patients infected with the human immunodeficiency virus (HIV) (approved in 1990)
   d. Reduction of allogeneic blood transfusion in surgical patients (approved in 1996)

2. Darbepoetin alfa indications:
   a. Patients with chronic kidney failure (approved in 2001)
   b. Patients with cancer on chemotherapy (approved in 2002)

A darbepoetin alfa registration study was conducted to assess anemia correction using both darbepoetin alfa and epoetin alfa.[26] This trial was a 24-week, multicenter, randomized, open-label study involving patients with CKD not on dialysis. Epoetin alfa was administered at one third less than the indicated dose. The initial doses of each agent could be reduced to maintain the target hemoglobin level. The initial dose of darbepoetin alfa (0.45 µg/kg administered once weekly) was reduced to 0.34 µg/kg (75% of initial dose) at week 24, and the initial dose of epoetin alfa (100 units/kg weekly, administered in 2 doses) was reduced to 56.9 units/kg (57% of initial dose) at week 24.

The target hemoglobin level was achieved in 93% of the 129 patients treated with darbepoetin alfa (94% in per protocol analysis) and in 92% of the 37 patients treated with epoetin alfa (100% in per protocol analysis). Initially, darbepoetin alfa demonstrated a slower hemoglobin response. When hemoglobin levels reached 14 g/dL in both groups, darbepoetin alfa and epoetin alfa were withheld until hemoglobin levels returned to 12 g/dL. Hemoglobin levels decreased more quickly among patients who received darbepoetin alfa, although the difference between groups was not statistically significant.

Once-weekly extended dosing of epoetin alfa has become a commonly used dosing regimen, and a recent trial verified the safety and efficacy of this schedule (Procrit® Once Weekly in Early Renal Insufficiency [POWER] trial).[27,28] This prospective, multicenter, open-



label study involved patients with CKD not on dialysis. Inclusion criteria included the following:

- S_{Cr} of 1.5-6.0 mg/dL (women) and 2.0-6.0 mg/dL (men)
- Baseline hemoglobin level ≤ 10 g/dL

Epoetin alfa (10,000 units) was administered subcutaneously (SC) once weekly for 16 weeks. A hemoglobin response was defined as an increase in hemoglobin of 1 g/dL from baseline. Outcomes included hemoglobin levels and hematocrit values, transfusion requirements, and quality of life (QOL), as measured by the Linear Analog Scale Assessment (LASA) and Kidney Disease Questionnaire (KDQ).

Hemoglobin levels and hematocrit values increased significantly from baseline. (See Table 5.) QOL improved significantly as measured by LASA and KDQ scores; hemoglobin level was the most significant predictor of QOL improvement. Transfusion requirements also decreased significantly.

Extended dosing schedules for darbepoetin alfa have also been studied. In 2 studies, darbepoetin alfa was initially dosed at 0.75 µg/kg every other week. The dose was then titrated, as necessary, to maintain a hemoglobin response (ie, 11.0 g/dL to 13 g/dL).[29-31] In the pilot study, 61 of 76 patients completed treatment. The median dose at the time of hemoglobin response was 60.0 µg (range, 30 µg to 130 µg), and the mean dose was not reported.[31] In the other study, 463 of 603 patients completed treatment. The mean dose at the time of hemoglobin response was 62.5 µg,[29] and the median dose was 60.0 µg (range, 5 µg to 100 µg).[30]

Although the pharmacokinetics of darbepoetin alfa appear to allow dosing regimens beyond its approved once-weekly administration, retrospective and prospective studies of

Table 5

POWER Clinical Trial: Outcomes

Time period	Mean hemoglobin (g/dL)	Mean hematocrit (%)
Baseline	9.1	27.5
Week 4	10.2*†	30.9*†
Week 8	11.2*†	34.2*†
Week 12	11.8*†	36.0*†
Week 16	11.8*	36.1*

*Significant change from baseline ($p < 0.0001$)
†Significant change from previous period ($p < 0.0001$)

N = 1,338

Provenzano R et al. Poster presented at: ASN; October 30-November 4, 2002; Philadelphia, Pa. Poster based on Abstract SU-P0037.

epoetin alfa demonstrate the same dosing flexibility, with a noteworthy dose decrease as intervals are extended.

Extended Dosing in a Real-world Setting

Extended dosing with epoetin alfa has been evaluated in a retrospective study at a private-practice clinic. Dosing once every 2, 3, or 4 weeks, or less frequently, was effective in achieving and maintaining target hemoglobin levels in patients with CKD.[32,33] (See Table 6.) The starting dose was once-weekly epoetin alfa 100 units/kg to 150 units/kg SC. When hemoglobin levels ranged from 11 g/dL to 12 g/dL for 2 consecutive laboratory values, dosing was decreased to once every 2 weeks, and the dose was increased by 50%. When hemoglobin levels ranged from 11 g/dL to 12 g/dL with this extended dosing, the dosing regimen was decreased to once monthly, again with a 50% increase in dose. The dosing interval for epoetin alfa was once every 2 weeks or less frequently in 90% of patients, once monthly in approximately 50% of patients, and even less frequently in some patients. As the dosing interval increased, the total monthly dose decreased.

This finding may be attributed to patient self-selection in which patients who are more responsive require less frequent dosing, although why patients have a greater or lesser response is not yet known. Hemoglobin levels were increased and maintained with extended dosing, with significantly higher levels associated with increased dosing intervals. Monthly use of epoetin alfa had no clear association with GFR. These results show that extended dosing with epoetin alfa is effective and practical for patients. Clinicians are afforded an opportunity to manage a larger number of patients, and patients are permitted a more convenient regimen.

Table 6

Extended Epoetin Alfa Dosing: Results From a Pre-ESRD Clinic

Dosing frequency	Mean monthly epoetin alfa dose (units)	Mean Hb level (g/dL)
Q 1 week	57,028	10.27
Q 2 weeks	44,886	11.10
Q 3 weeks	28,072	11.71
Q 4 weeks	17,542	12.03

Pisoff S et al. Poster presented at: ASN/ISN World Congress of Nephrology; October 13–17, 2001; San Francisco, Calif.
Pisoff S et al. J Am Soc Nephrol. 2001;12:407A (Abstract A3998).

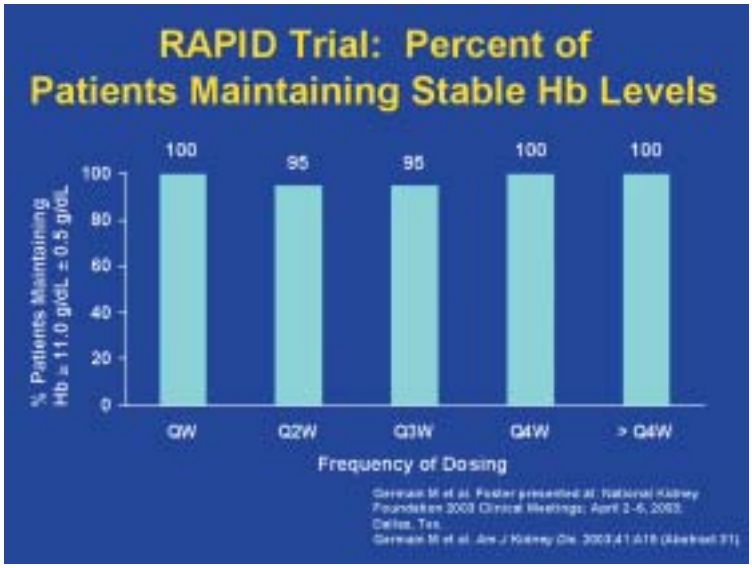
"We found that approximately 90% of our patients could be dosed with epoetin alfa at 2-week intervals or less frequently, and about half of our patients were dosed once monthly." — *Michael J. Germain, MD*

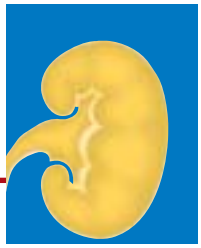
Extended Dosing in Clinical Trial Settings

These results in a private-practice clinic were substantiated in a larger, multicenter study, the Retrospective Review of Alternate Procrit® Dosing (RAPID) trial.[34,35] The clinical usage and efficacy of extended epoetin alfa dosing were examined in patients being treated for anemia associated with CKD. This study was a retrospective chart review of 200 patients not yet on dialysis. Patients had anemia of CKD, S_{Cr} levels of 1.5 to 6.0 mg/dL (women) or 2.0 to 6.0 mg/dL (men), and stable hemoglobin levels (≥ 11 ± 0.5 g/dL) maintained with epoetin alfa once every 2, 3, or 4 weeks for at least 3 months. Interim results for 110 patients were presented at the 2003 NKF Clinical Meetings. There was no clear correlation between S_{Cr} and dosing frequency. The mean monthly epoetin alfa dose decreased as the dosing interval increased; this difference was substantial. Stable hemoglobin levels were maintained in nearly all patients at all dosing frequencies. (See Figure 3.)

These results are being further evaluated in a prospective, multicenter trial, which is assessing the safety and efficacy of extended epoetin alfa dosing in patients with CKD (Procrit® for Maintenance Phase Treatment [PROMPT] of patients with anemia due to CKD). Patients are randomized into 1 of 4 dosing regimens of epoetin alfa: 10,000 units SC every week, 20,000 units SC every 2 weeks, 30,000 units SC every 3 weeks, and 40,000 units SC every 4 weeks. Approximately 500 CKD patients at approximately 100 sites are being evaluated; they have stable hemoglobin levels (≥ 11 g/dL) and have

Figure 3



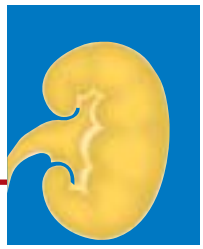


been receiving epoetin alfa for at least 2 months. The primary efficacy evaluation is maintenance of hemoglobin level; the secondary efficacy evaluation is QOL as assessed by LASA and KDQ.

In pre-dialysis patients, studies show that it is possible to extend dosing schedules of epoetin alfa to once every month or even less frequently; such dosing schedules should allow nephrologists to see more patients more efficiently.[26-35]

Key Points

In pre-dialysis patients, it has been shown that extended dosing schedules of epoetin alfa (from once weekly to once monthly or even less frequently) are efficacious and safe with an observed dose decrease as intervals are extended. Darbepoetin alfa has been examined similarly in dosing regimens beyond its approved once-weekly administration. Retrospective and prospective studies of epoetin alfa and darbepoetin alfa have shown the same dosing flexibility, permitting more efficient management of patients with anemia of CKD.



In Patients With CKD, What Is the Target Hemoglobin Level?

The Correction of Hemoglobin and Outcomes in Renal Insufficiency [CHOIR] Trial

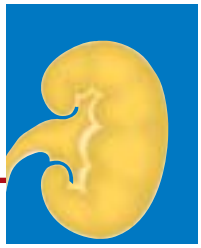
Although it has become evident that hemoglobin can be effectively increased with epoetin alfa, the ideal hemoglobin level is still unclear.[5] The burning question concerns the target hemoglobin level: What should it be? Studies to date have been small; consequently, they cannot address this question adequately. The Correction of Hemoglobin and Outomes in Renal Insufficiency (CHOIR) study was designed to answer this question and determine the effect of correction of anemia on cardiovascular outcomes and all-cause mortality in patients with CKD.

By comparing the outcomes of patients with CKD randomly assigned to 2 treatment groups, which differ only in targeted hemoglobin levels, this study will test the hypothesis that the level of anemia correction with once-weekly dosing of epoetin alfa will decrease mortality and cardiovascular morbidity. Primary outcomes will be a composite of all-cause mortality, myocardial infarction, stroke, and hospitalization for congestive heart failure (CHF). Secondary outcomes will include RRT, all-cause hospitalizations, and changes from baseline in hemoglobin/hematocrit, epoetin alfa dose, nutritional status, and health-related quality of life (HRQOL). Additionally, an echocardiographic substudy will assess the effect of anemia correction on LV geometry and function.

In Phase 1, CHOIR intends to enroll 1,350 patients at 150 sites. Patients ≥ 18 years of age with CKD (defined as GFR ≥ 15 mL/min/1.73 m^2 and ≤ 50 mL/min/1.73 m^2; GFR calculated from the MDRD equation) and a hemoglobin (Hb) level < 11 g/dL at study entry will be assigned randomly to 1 of 2 treatment groups:

A. Therapy to maintain Hb as close to 13.5 g/dL as possible
B. Therapy to maintain Hb as close to 11.3 g/dL as possible

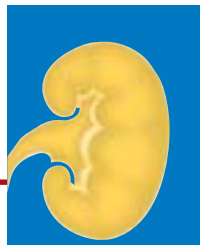
Phase 2 involves patient intervention for up to 36 months or until the start of RRT, and Phase 3 is the closeout (3 months). Epoetin alfa initially will be administered as a once-weekly dose of 10,000 units SC, reflecting the current standard of care. After the initial 3 once-weekly doses, subsequent doses and dosing regimens will be adjusted based on the 2 most recent Hb values. To revise dosing, investigators will use dosing algorithms specified in the protocol. The maximum permitted dose will be 20,000 units. Patients achieving stable, target Hb levels will be allowed every-2-week dosing and visits. They will receive epoetin alfa either up to the initiation of RRT or until completion of the 36-



month period. CHOIR intends to finally answer the questions: In patients with CKD, can anemia correction with epoetin alfa decrease mortality and cardiovascular morbidity? What should be the target hemoglobin level?

Concluding Remarks

- Anemia and CVD are prevalent in patients with CKD.
- Treatment of anemia and CVD is important to optimize outcomes.
- A collaborative approach to patient care can have a positive effect on outcomes.
- Extended dosing intervals of erythropoietic agents have been found to be safe and effective; future research will further clarify optimal dosing regimens.



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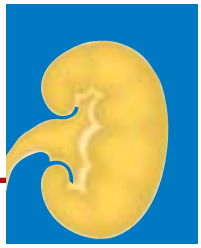

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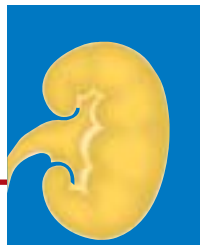


Faculty Biographies and Disclosure Statements

Ajay K. Singh, MD, MRCP, MBA

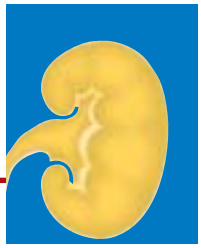
Ajay K. Singh is Clinical Director of the Renal Division of Brigham and Women's Hospital, Boston, and an Associate Professor of Medicine at Harvard Medical School. Dr. Singh received his medical degree from University College Hospital in London. He completed his internship at Stafford General Infirmary and Stoke Mandeville Hospital and his residency at Southeast Hospital in the United Kingdom. He then completed a fellowship at the Tufts-New England Medical Center in Boston. In addition to his degree in medicine, Dr. Singh holds a master's degree in business administration from the Boston University School of Management. Dr. Singh is a member of several professional organizations, including the Royal College of Physicians of London, the American Society of Nephrology (ASN), the International Society of Nephrology and the National Kidney Foundation. He is the Co-Chair of the 2003 Committee for the ASN and the Program Committee for the Renal Physicians Association. Dr. Singh has written more than 80 scientific articles, abstracts and book chapters in the field of nephrology.

Disclosure Statement

Dr. Singh has been a consultant and has received research support from Ortho Biotech Products, L.P.

Paul L. Kimmel, MD

Paul L. Kimmel has served on the faculty of the George Washington University Medical Center, Washington, DC, since 1983. Currently, he is Professor of Medicine and Director of the Division of Renal Diseases and Hypertension, Department of Medicine. Dr. Kimmel received his medical degree from the New York University School of Medicine. He trained in internal medicine and nephrology at Bellevue Hospital, New York, and the Hospital of the University of Pennsylvania in Philadelphia. His research interests have included sleep disorders in patients with end stage renal disease (ESRD), zinc metabolism and its association with mineral and vitamin D metabolism in chronic kidney disease, the pathogenesis and therapy of HIV-associated kidney disease, psychological adaptation in chronic kidney disease and cytokine biology in dialysis patients. Dr. Kimmel has investigated the association of hematocrit and circulating cytokines in ESRD patients treated with erythropoietin, and he has collaborated with the federal government and the private sector to analyze the



use of erythropoietin in the ESRD program in the United States. He has a long-standing interest in the assessment of quality of life in hemodialysis patients and its association with biological factors. In addition, Dr. Kimmel has served on the editorial boards of *Blood Purification,* the *American Journal of Kidney Diseases* and the *Journal of the American Society of Nephrology.*

Disclosure Statement

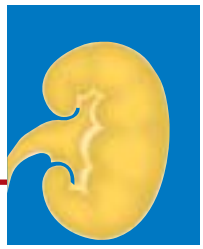
Dr. Kimmel is a consultant and member of the steering committee for the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study sponsored by Ortho Biotech Products, L.P.

Michael J. Germain, MD

Michael J. Germain is the Medical Director of Renal Transplantation, Western New England Renal and Transplant Associates, Springfield, Massachusetts; an Associate Professor of Medicine at Tufts University School of Medicine, Boston; and a Clinical Professor of Medicine at Springfield College. Dr. Germain is a consultant for several hospitals including Baystate Medical Center, Springfield, Massachusetts; Franklin Medical Center, Greenfield, Massachusetts; and Mary Lane Hospital, Ware, Massachusetts. He is also a member of the research committee at Baystate Medical Center. Dr. Germain received his medical degree from the University of Calgary in Alberta, Canada. Both his internship and residency in internal medicine were completed at Cambridge Hospital, Cambridge, Massachusetts. Dr. Germain completed his fellowship in nephrology at Hennepin County Medical Center, Minneapolis, Minnesota. Dr. Germain's research interests and publications include renal palliative care, exercise in CKD patients and predictive value of GFR measurements in kidney transplant patients.

Disclosure Statement

Dr. Germain has been a consultant and speaker for Ortho Biotech Products, L.P.



Instructions for Obtaining CME/CE Credits

For CME/CE credit, please follow the instructions below and submit required items no later than January 24, 2006.

Post-test Instructions

Complete the post-test on page 27, using the answer form found in the enclosed, postage-paid return envelope. Read each test question carefully and select the answer you believe to be correct. There is only one best choice for each question. Indicate your answer for each question by filling in the appropriate circle on the answer form.

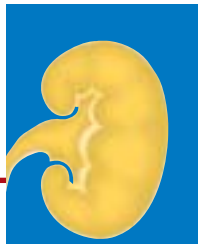
Complete the program evaluation, which you will find on the answer form. **You must submit a completed evaluation in order for your post-test and CME/CE request to be processed.**

Fill in all pertinent contact information as requested on the answer form. Please print legibly.

Submit the form in the enclosed, postage-paid return envelope. Please make sure all sections have been completed. Mail to:

National Kidney Foundation
30 East 33rd Street
New York, NY 10016
Attention: Kidney Learning System (KLS)™ Coordinator

You must achieve a score of at least 75% in order to obtain CME, CPE or CE credit. You may retake the post-test if you score below 75%. You may obtain another post-test answer form by calling (800) 622-9010, ext. 239. Please keep a copy of the monograph and test should you need to retake the exam. After successful completion of this program, the National Kidney Foundation will mail you a CME, CPE or CE certificate as well as the test answers. The monograph and post-test may also be accessed on the KLS™ Web site **www.nkfkls.org**



Post-test

The following test will help you review the information presented in this monograph.

There is only one best answer to each question. Please mark your answer on the post-test answer form, which you will find in the enclosed, postage-paid envelope.

1. The number of American adults who have chronic kidney disease is:

   A. 300,000
   B. 40 million
   C. 20 million
   D. 13 million

2. The K/DOQI classification of chronic kidney disease is based on:

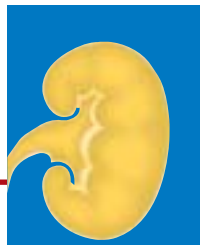
   A. Age of the patient
   B. Serum creatinine
   C. GFR and presence or absence of kidney damage
   D. BUN

3. In Stage 4 CKD, anemia is present in:

   A. 50% of patients
   B. 5% of patients
   C. 15% of patients
   D. 1%-2% of patients

4. The K/DOQI CKD guidelines recommend that clinicians take steps to reduce cardiovascular risk starting in:

   A. Stage 1
   B. Stage 2
   C. Stage 3
   D. Stage 4



5. Which of the following statements about earlier referral to nephrologists is *not* true?

A. It results in decreased morbidity and mortality
B. It promotes successful permanent vascular access
C. It is associated with lower hemoglobin levels
D. It leads to increased pre-dialysis use of erythropoietic agents

6. Which of the following statements about collaborative care is *not* true?

A. It results in fewer days in the hospital for patients
B. It leads to cost savings
C. It results in less outpatient education
D. It is associated with fewer urgent dialysis starts

7. A collaborative care approach would include:

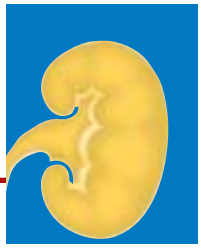
A. Primary care physicians
B. Nurse practitioners
C. Dietitians
D. All of the above

8. Studies show extended dosing of erythropoietic agents is effective at:

A. 2-week intervals
B. 3-week intervals
C. 4-week or longer intervals
D. All of the above

9. One of the goals of the CHOIR study is to determine:

A. The lowest effective dose of epoetin alfa
B. The best time to start treating anemia in CKD patients
C. The optimal interval for extended dosing
D. What the ideal target hemoglobin should be



10. NKF's KEEP program is designed to:

    A. Provide workshops for new dialysis patients
    B. Promote early identification of people at increased risk for CKD
    C. Develop clinical practice guidelines for CKD management
    D. Develop educational programs for patients and clinicians

11. The percent of CKD patients who have CVD is:

    A. 15%
    B. 50%
    C. 10%
    D. 25%

12. Studies show anemia correction can delay CVD progression by:

    A. Delaying the need to start RRT
    B. Increasing exercise tolerance
    C. Reducing LV mass index
    D. Improving patients' appetites

13. As extended dosing intervals increase, the dose of epoetin alfa agents usually:

    A. Increases
    B. Decreases
    C. Stays the same
    D. Varies

14. A decrease of 0.5 g/dL in hemoglobin increases the risk of left ventricular growth by

    A. 10%
    B. 6%
    C. 25%
    D. 32%

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