IV. NKF-K/DOQI CLINICAL PRACTICE GUIDELINES FOR ANEMIA OF CHRONIC KIDNEY DISEASE: UPDATE 2000

NOTE: The citation for these guidelines should read as follows: National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease, 2000. Am J Kidney Dis 37:S182-S238, 2001 (suppl 1)

Acronyms and Abbreviations

Abbreviation	Term
AIDS	acquired immune deficiency syndrome
BSA	body surface area
CAPD	continuous ambulatory peritoneal dialysis
CBC	complete blood count
CKD	chronic kidney disease
CRF	chronic renal failure
EPO	erythropoietin
ESRD	end-stage renal disease
FDA	Food and Drug Administration
Fe	iron
GFR	glomerular filtration rate
HCFA	Health Care Financing Administration
Hct	hematocrit
Hgb	hemoglobin
IP	intraperitoneal
IV	intravenous
LVH	left ventricular hypertrophy
PD	peritoneal dialysis
PET	positron-emission tomography
PMMA	polymethylmethacrylate
PTFE	polytetrafluoroethylene
RBC	red blood cell
SC	subcutaneous
SLE	systemic lupus erythematosus
TIBC	total iron binding capacity
TSAT	transferrin saturation
USRDS	United States Renal Data System

Introduction

ANORMOCYTIC, normochromic anemia is present in the majority of patients who have a reduction in kidney function.[3] The same pathophysiology underlies this anemia in all such patients. In these guidelines, the term "chronic kidney disease" (CKD) is used to describe patients with chronically reduced kidney function, including those with chronic allograft dysfunction, and those in kidney failure who are dialysis dependent (administratively termed ESRD). When untreated, the anemia of CKD is associated with a number of physiologic abnormalities, including decreased tissue oxygen delivery and utilization,[4-8] increased cardiac output, cardiac enlargement, ventricular hypertrophy, angina, congestive heart failure,[9-14] decreased cognition and mental acuity,[15] altered menstrual cycles,[16-18] decreased nocturnal penile tumescence,[19] and impaired immune responsiveness.[20,21] In addition, anemia may play a role in growth retardation and decreased intellectual performance in pediatric patients.[22,23] These abnormalities reduce quality of life[24] and opportunities for rehabilitation of CKD patients and decrease patient survival.[25]

The primary cause of anemia in patients with CKD is insufficient production of erythropoietin (EPO) by the diseased kidneys.[26] Additional factors which may cause or contribute to the anemia include: iron deficiency,[27] either related to or independent of blood loss from repeated laboratory testing, needle punctures, blood retention in the dialyzer and tubing, or gastrointestinal bleeding; severe hyperparathyroidism[28]; acute and chronic inflammatory conditions[29]; aluminum toxicity[30]; folate deficiency[31]; shortened red blood cell survival[32]; hypothyroidism[33]; and hemoglobinopathies such as α-thalassemia.[33] These potential contributing factors, if relevant, should be considered and addressed.

Recombinant human erythropoietin (rHuEPO) has been used in the treatment of the anemia of CKD since 1986.[34,35] This recombinant hormone has been referred to by several names, including rHuEPO, EPO, Epoetin, Epoetin alfa, Epoetin beta, and erythropoietin. Epoetin alfa (manufactured by Amgen Inc, Thousand Oaks, CA; distributed in the United States as Epogen by Amgen, Inc, and as Procrit by Ortho Biotech, Johnson & Johnson) is the only approved recombinant human erythropoietin (rHuEPO) product available in the United States. In addition to Epoetin alfa, Epoetin beta, another rHuEPO product with similar pharmacologic effects, is available in other countries but not the United States. Clinical trials with both Epoetin alfa and Epoetin beta have been performed within and outside of the United States, and the clinical response to both has been similar. These guidelines for the management of anemia are based upon available literature for both products. Since these guidelines may be used outside as well as within the United States, the term "Epoetin," when used throughout the guidelines, should be assumed to apply to both Epoetin alfa and beta. Situations that apply only to Epoetin alfa are clearly indicated.

A new erythropoietin-like molecule, called NESP, or novel erythropoietic stimulating protein (manufactured by Amgen, Inc), is being used in clinical trials and as of July 2000 is being reviewed by the FDA. NESP is a glycoprotein similar to erythropoietin, but has 5 additional amino acids in its primary sequence and two extra N-linked carbohydrate side chains, giving it a longer plasma half-life. There have been no peer-reviewed clinical studies published about this molecularly engineered hormone prior to January 2000 when the structured literature review of this update was closed.

Iron is also essential for hemoglobin formation. The iron status of the patient with CKD must be assessed and adequate iron stores should be available before Epoetin therapy is initiated. Iron supplementation usually is essential to assure an adequate response to Epoetin in patients with CKD because the demands for iron by the erythroid marrow frequently exceed the amount of iron that is immediately available for erythropoiesis (as measured by percent transferrin saturation) as well as iron stores (as measured by serum ferritin). In most cases, intravenous iron will be required to achieve and/or maintain adequate iron stores. In the United States as of July 1999, the commercially available intravenous iron preparations consist of iron dextran, manu-

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factured as INFeD by Watson Pharmaceutical, Inc, Nephrology Division (formerly Schein Pharmaceutical, Inc.) and as Dexferrum by American Regent Laboratories Inc and sodium ferric gluconate complex in sucrose (referred to in this text as iron gluconate), manufactured as Ferrlecit by R & D Laboratories and marketed by Watson Pharmaceutical, Inc, Nephrology Division (formerly Schein Pharmaceutical, Inc.). An additional intravenous iron preparation, iron sucrose (Venofer, manufactured by American Regent Laboratories, Inc), was approved by the FDA in November 2000. The molecular weights of the two iron dextran compounds differ, and they will be considered different compounds.

Effective treatment of the anemia of CKD improves survival,[36] decreases morbidity,[37,38] and increases quality of life.[24,39] These 27 clinical practice guidelines, which cover the diagnosis, work-up, and management of the anemia of CKD, as well as possible sequelae related to its therapy, provide information that will help caregivers accomplish these goals. Unless otherwise specified, these guidelines, and their rationales, apply to all age groups.

The potential impact of these guidelines on aggregate use of Epoetin is unknown. For example, these guidelines recommend a higher target Hgb/Hct than is used in current practice and than has been recommended on the basis of an evaluation of evidence performed by Canadian nephrologists.[40] All other things being equal, this recommendation would increase the amount of Epoetin required. On the other hand, the guidelines also have recommended maintenance of iron stores for the support of erythropoiesis that are greater than those maintained in current practice. This recommendation should produce an Epoetin-sparing effect. In addition, the guidelines recommend that Epoetin be administered by the subcutaneous (SC) route to most patients. This should provide an improved Hgb/Hct response for the same Epoetin dose, again producing an Epoetin-sparing effect. The likely net impact of these different effects is difficult to predict.

Some of the practices recommended in these guidelines are at variance with current policy of the Health Care Financing Administration (HCFA) and with information contained in the package inserts for Epoetin (Guideline 25) and iron dextran (Guideline 9). In these instances, the Anemia Work Group believes there is sufficient published scientific data to justify its recommendations. In most circumstances, recommendations contained in this document are based on evidence from the medical literature.

When recommendations are based on evidence, a rationale and supporting literature references are indicated. When recommendations are based on opinion in the absence of published evidence, the rationales for the recommendations are described. In some instances, however, recommendations are based in whole or in part on the opinion of the Work Group members. The evidentiary basis (published evidence, opinion, or both) for all recommendations is clearly indicated, along with the rationale (chain of reasoning) for each recommendation.

I. Anemia Work-Up

GUIDELINE 1

When to Initiate the Work-Up of Anemia

An anemia work-up should be initiated in patients with chronic kidney disease (CKD) when the:

- Hgb <11g/dL (Hct is <33%) in pre-menopausal females and pre-pubertal patients (**Evidence**)
- Hgb <12g/dL (Hct is <37%) in adult males and post-menopausal females (**Evidence**)

Rationale Anemia is defined in terms of the Hgb or Hct concentration. In this guideline, we recommend that a work-up of anemia be initiated when the Hgb/ Hct level declines to approximately 80% of the mean level for defined healthy, normal subgroups (see Table IV-1: eg, in females, 80% of Hct 41 = Hct 33; in males, 80% of Hct 47 = Hct 37). Differences in average Hgb/Hct levels between adult men and women are likely due to differences in estrogen and testosterone production that emerge at puberty, but subside after menopause. Anemia is likely to be present in individuals when Hgb/ Hct concentrations are below these levels. However, the mean Hgb/ Hct in the general population is only a statistical benchmark and may not be the best indication of anemia in every individual. For example, there is a 75% likelihood of anemia in an adult female with a Hct of 34% or a Hgb of 11 g/dL, or in a male with a Hct of 39% or a Hgb of 12.5 g/dL. Moreover, many individuals have Hgb/Hct concentrations which are physiologically normal for them, but which would be defined as anemia in terms of the general population data. Others have a Hgb/Hct level that may be physiologically inadequate for them (eg, patients with chronic obstructive pulmonary disease), even though it falls within the range considered normal for the general population.

In hemodialysis patients, blood samples to document and monitor anemia should be obtained prior to or immediately upon initiation of the dialysis procedure (predialysis). While a Hgb/ Hct obtained at the end of the dialysis procedure (postdialysis) may relate better to a patient's estimated dry weight, experience and data reported in the literature universally refer to predialysis Hct and Hgb levels; hence the need to relate these guidelines to predialysis blood samples.

An automated cell counter should be used to determine RBC indices, Hct, and Hgb because the results are more easily standardized. Automated cell counters also have the advantage of providing a total white blood cell count and, often, a platelet count.

Outside of the United States, Hgb, rather than Hct, is used to quantify the level of anemia in patients with CKD. There are several reasons why Hgb is a more accurate, and hence better measure of anemia than is Hct. First, whereas Hgb is stable when a blood sample is stored at room temperature, Hct is not. Specifically, MCV (from which Hct is calculated: MCV × erythrocyte count = Hct) is stable at room temperature for only 8 hours and is stable for only 24 hours when a blood sample is refrigerated.[41] When a blood sample is stored for longer periods of time, MCV increases, resulting in increases in calculated Hct by as much as 2% to 4%.[42] In contrast, Hgb remains unchanged when a blood sample is stored for the same amount of time under the same conditions.[42] The sensitivity of Hct to blood sample storage conditions is particularly important in light of increased consolidation in the dialysis industry in the United States and the resulting tendency for dialysis centers that comprise a given dialysis chain to ship blood samples over variable distances, under poorly controlled conditions, to centralized laboratories.

A second reason why Hgb is a more accurate measure than Hct is that in the presence of hyperglycemia, MCV (but not Hgb) is falsely elevated, resulting in a false elevation of calculated Hct.[43,44] Finally, there is greater variability across automated analyzers in estimation of the number and size of erythrocytes that are in a blood sample (and hence in calculation of Hct) than there is in measurement of Hgb.[45] Data comparing the within-run and between-run coefficient of variation (CV) in automated analyzer measurements have shown that these CVs for measurement of Hgb are one half and one third those for Hct, respectively.[46]

For all these reasons, Hgb is a better measure to use to monitor and manage anemia in patients with CKD than is Hct, particularly given the

Table IV-1. Mean Normal Values of Hemoglobin and Hematocrit for the Healthy, Normal Population[47]

Age/Gender	Hemoglobin (g/dL)	Hematocrit (%)
Birth	16.5 ± 3.0	51 ± 9
1 month	14.0 ± 4.0	43 ± 6
2 to 6 months	11.5 ± 2.5	35 ± 7
6 months to 2 years	12.0 ± 1.5	36 ± 3
2 to 6 years	12.5 ± 1.0	37 ± 3
6 to 12 years	13.5 ± 2.0	40 ± 5
12 to 18 years (male)	14.5 ± 1.5	43 ± 6
Menstruating female	14.0 ± 2.0	41 ± 5
Adult male/post-menopausal female	15.5 ± 2.0	47 ± 6

growing tendency for dialysis centers to send blood samples to outside laboratories, rather than measuring Hgb or Hct in-house. In addition, use of hemoglobin will allow better comparison of anemia management between countries, since most other countries use measurement of hemoglobin as the standard. Therefore, the Anemia Work Group strongly urges that hemoglobin be the primary means of quantifying the level of anemia in patients with CKD.

GUIDELINE 2

Anemia Evaluation

A. Evaluation of anemia should consist of measurement of at least the following: (**Evidence**)

- Hemoglobin (Hgb) and/or Hematocrit (Hct)
- Red blood cell (RBC) indices
- Reticulocyte count
- Iron parameters:
  - —Serum iron
  - —Total Iron Binding Capacity (TIBC)
  - —Percent transferrin saturation (serum iron × 100 divided by TIBC) [TSAT]
  - —Serum ferritin
- A test for occult blood in stool
- B. This work-up should be performed before Epoetin therapy is begun. (**Opinion**)

Rationale The red blood cell indices, reticulocyte count (an index of new red blood cell formation), and iron parameters are helpful to detect the cause of many anemias which are not due to EPO deficiency.[48] The anemia of CKD is generally normocytic and normochromic. Microcytosis may reflect iron deficiency, aluminum excess, or certain hemoglobinopathies; macrocytosis may be associated with vitamin B12 or folate deficiency. Macrocytosis can also be associated with iron excess[49] and/or Epoetin therapy that shifts immature, larger reticulocytes into circulation. An elevated reticulocyte count (corrected for the degree of anemia) suggests that active hemolysis may be present, such as in acute renal failure due to the hemolytic uremic syndrome. An abnormal white blood cell count and/or platelet count may reflect a more generalized disturbance of bone marrow function, such as that due to malignancy or vasculitis.

Iron is critical for Hgb synthesis. Consequently, patients should be carefully evaluated for the availability of iron, by measuring the serum iron and the TIBC. The serum iron and the percent TSAT reflect the amount of iron immediately available for hemoglobin synthesis. The serum ferritin reflects total body iron stores. A low level of either of these indices may indicate the need for supplemental iron to support erythropoiesis. Iron deficiency has been shown to be present in as many as 25% to 37.5% of patients presenting with the anemia of CKD[50,51] and, if treated, can at least temporarily improve or correct the anemia[52] (Endnote a). Absolute iron deficiency in the general population is indicated by a TSAT of less than 16%[53] and/or a serum ferritin value of less than 12 ng/mL.[54] However, higher values of TSAT and serum ferritin may be necessary to achieve an erythropoietic response prior to initiation of Epoetin therapy (Endnote a) and higher values for these parameters will be required to support accelerated erythropoiesis stimulated by pharmacological administration of Epoetin (see Guideline 6: Target Iron Level). The presence of iron deficiency requires a search for the cause, which is usually blood loss. A stool guaiac test for occult blood is recommended to test for gastrointestinal bleeding in patients with iron deficiency. Another test for early iron deficiency is an increase in the number of hypochromic red blood cells determined by certain autoanalyzers, ie, Technicon H-1, H-2, and H-3 Autoanalyzers (Bayer Diagnostics). A hypochromic red blood cell is defined as an individual cell with an Hgb concentration of <28 g/dL. Normally, less than 2.5% of red blood cells are hypochromic. Although the autoanalyzer used to

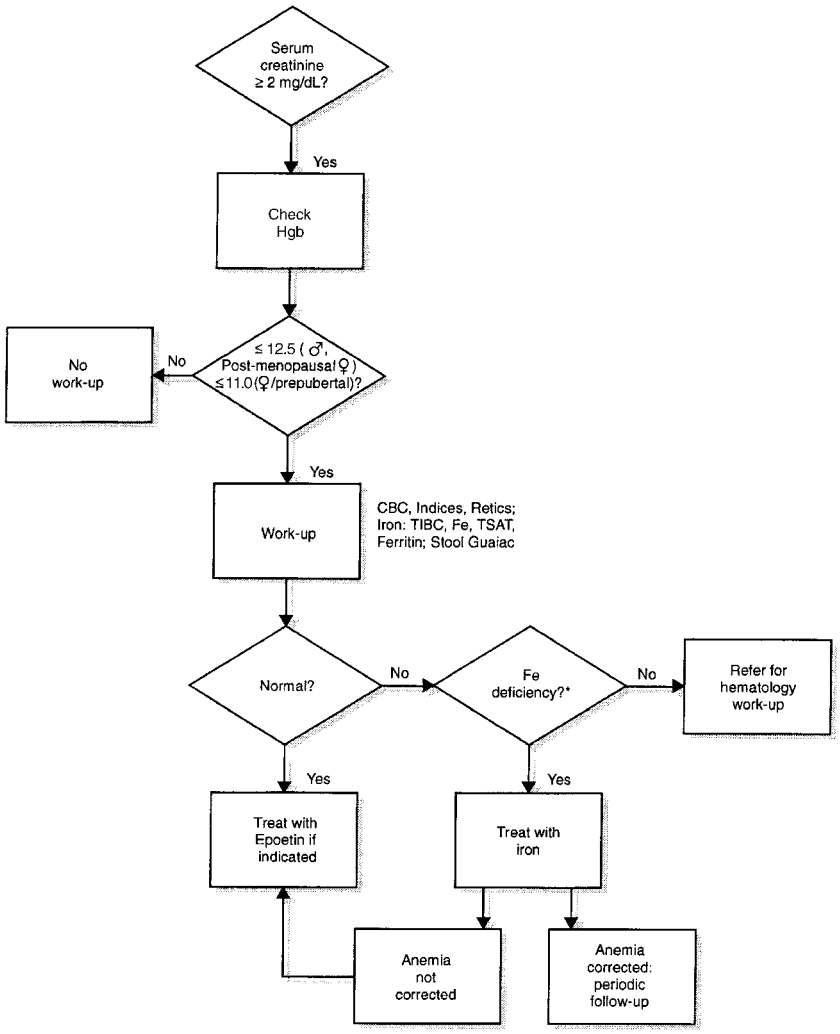

Fig IV-1. Anemia work-up for CKD patients. Asterisk indicates that laboratory values are consistent with uncomplicated iron deficiency.

perform this test is available in Europe,[55,56] it is not readily available in the United States at this time. Because of the limited availability of these autoanalyzers in the United States, this test has not been included as part of the guideline. However, if such technology becomes routinely available in the United States, this test should be considered in the work-up of the anemia of CKD, particularly since Epoetin therapy may increase the likelihood of functional iron deficiency.

In CKD patients without iron deficiency, it is prudent to screen for common causes of anemia other than EPO deficiency (see Guideline 3: Erythropoietin Deficiency). Correcting an easily reversible cause of anemia makes both clinical and economic sense. An example is hypothyroidism, which is common in the general population, and can cause a normochromic, normocytic anemia that can mimic the anemia due to EPO deficiency.[33] If a reversible cause of anemia is not present or has been corrected, and EPO deficiency is the likely primary cause of the anemia, then anemia should be treated with Epoetin to improve patient quality of life,[24] to improve the various physiological abnormalities associated with anemia, to decrease morbidity,[37] to decrease hospitalization,[57] and to improve patient survival.[36]

GUIDELINE 3

Erythropoietin Deficiency

If no cause for anemia other than CKD is detected, based on the work-up outlined in Guideline 2: Anemia Evaluation, and the serum creati-

nine is ≥2 mg/dL, anemia is most likely due to EPO deficiency. Measurement of serum EPO levels usually is not indicated. Fig IV-1 provides a guideline for the work-up of anemia in patients with a serum creatinine ≥2 mg/dL, and for those occasional patients with a lower serum creatinine and impaired kidney function who have a normocytic, normochromic anemia. (**Evidence**)

Rationale As kidney function declines, the likelihood of anemia associated with EPO deficiency increases because the diseased kidneys are unable to produce sufficient quantities of EPO. Anemia can develop relatively early in the course of CKD, however, and has been associated with a serum creatinine as low as 2.0 mg/dL,[58] and occasionally even lower, particularly in individuals with a reduced muscle mass. On the other hand, there is a wide range of Hgb/Hct levels for any degree of kidney dysfunction. Two studies have found a linear relationship between Hct and creatinine clearance in pediatric patients. A linear relationship between GFR and Hct was observed in 48 pediatric patients in one study,[59] and in 31 CKD pediatric patients in another study when the GFR was estimated from the serum creatinine.[60] In these two studies, significant anemia was noted when the GFR was less than 20 and 35 mL/min/1.73 m^2, respectively.

The anemia of CKD should not be confused with the anemia of chronic disease. In the latter, inflammatory cytokines suppress the endogenous production of EPO and erythropoiesis directly.[61,62] Measurable levels of circulating cytokines may be found in stable dialysis patients, but, in the absence of inflammation, do not appear to adversely affect the action of Epoetin[63,64] (see Guideline 20: Causes for Inadequate Response to Epoetin).

In patients with non-renal anemia, serum EPO levels are usually elevated in an effort to compensate for the anemia. In patients with impaired kidney function and a normochromic, normocytic anemia, it is rare for the serum EPO level to be elevated. Therefore, measurement of EPO levels in such patients is not likely to guide clinical decision-making or Epoetin therapy.

Figure IV-1 suggests an approach for evaluating anemia in CKD patients who do not have gastrointestinal bleeding.

II. Target Hemoglobin/Hematocrit

BACKGROUND

The initial patient experience with Epoetin came in a Phase I-II clinical trial in hemodialysis patients with the anemia of CKD. The target maintenance Hct for these patients was 35% to 40%, ie, at the lower range of normal.[35] When investigators met to design the Phase III multicenter clinical trial, hematologists argued that the target Hct should be a normal Hct, while nephrologists proposed a lower level. A compromise target Hct of 35% was used in the trial. The final Hct levels for the more than 300 patients treated with Epoetin in the Phase III trial ranged from 33% to 38%. The results of this study,[65] together with those of the Phase I-II clinical trial, were submitted to the FDA. The FDA approved Epoetin therapy in June, 1989, but the target Hct range recommended by the FDA was only 30% to 33%, for reasons that have never been clear. The FDA recommendation is probably responsible for the previously held belief that a target Hct of 30% to 33% is medically appropriate. In spite of the FDA's decision in June 1994 to widen the target hematocrit range to 30% to 36%, the USRDS data derived from practice in 1993 (United States Renal Data System 1996 Annual Data Report)[66] showed that the mean Hct for Epoetin-treated dialysis patients in the United States was still in the lower end of this target range (30.2%), with 43% of patients having Hct values $<$30%. By the end of 1997 the mean Hct increased to 32.4% (USRDS 1999 Annual Data Report).[67]

Most of the initial physiologic and quality of life studies of anemic predialysis and dialysis patients treated with Epoetin in the United States had target Hct values of $\geq$36%. Virtually all studies have shown that, with increased Hct, there is marked improvement in various physiologic measures—oxygen utilization [VO_2][4-8]; muscle strength and function[68]; cognitive and brain electrophysiological function[15]; cardiac function[9,12-14,69,70]; sexual function[18]; or quality of life.[24] While two reports have cautioned that a target Hct greater than 30% could result in clotting of various arteries, as well as underdialysis,[71,72] these predictions have failed to materialize or be substantiated. Two other groups of investigators reported that there were no differences in various physiologic and quality of life measures between hemodialysis patients with Hct (or Hgb) levels of 30% (9 to 10 g/dL) versus 36% (11 to 12 g/dL).[73-75] However, a re-examination of these data allows for a different conclusion: the data are difficult to interpret in one study, and some physiological parameters were better at the higher Hgb/Hct in the other study (Endnote b). The authors of one of these studies have recently completed various physiological and quality of life studies in a small number of hemodialysis patients and have clearly shown that a normal Hgb (14 g/dL) is superior to a Hgb of 10 g/dL.[76-79]

Since 1989, when the FDA established its guidelines for the target Hct, and the Health Care Financing Administration (HCFA) established a policy under which it would not reimburse dialysis centers for the use of Epoetin when the Hct was above 36%, there have been few studies published in the United States which examine whether a Hct higher than 36% is more beneficial than a Hct of 30% in dialysis patients. While there are many studies that have shown the benefits of Hct values $\geq$36%, in most cases the comparison was made to outcomes of patients with an Hct level of $<$25% (see above). In order to formulate our recommendations regarding the target Hgb/Hct, the Anemia Work Group reviewed only peer-reviewed studies that compared baseline Hgb/Hct levels of 10 to 11 g/dL/30% to 33% (which is the current target level in the United States and most other countries) to higher values. Review of the literature which involved predialysis and dialysis patients within and outside the United States showed that, compared to higher Hgb/Hct values, Hgb/Hct values 11 g/dL/$<$33% are associated with increased morbidity and mortality. In addition, a number of recent United States and non-United States studies reported in abstracts indicate that patients with CKD function better at Hct levels that are near normal or normal and that improvement is continuous as the Hgb/Hct increases above 10 g/dL/30% to normal levels. The only exception to this has been a study sponsored by Amgen that involved more than 1,200 hemodialysis patients with documented heart disease. This study was discontinued when it appeared that those patients

randomized to a target Hct in the normal range (42% ± 3%) were experiencing a greater incidence (30%, with a confidence interval of 0.9 to 1.9) of non-fatal myocardial infarctions or death than did the control group randomized to a target Hct of 30% ± 3%.[80] The difference was not statistically significant at the time the study was terminated, however. Additional studies are needed to clarify the relationship between Hgb/Hct and outcomes in CKD patients, particularly those with heart disease. Such studies should be designed to determine the highest Hgb/Hct that provides incremental benefits without serious side effects. Several multicenter studies addressing this question are in progress outside the United States. A study determining whether the "prevention" of anemia and its associated adverse effects could also be of value, since one of the aims of treating anemia is to prevent or retard the development of heart disease.

GUIDELINE 4

Target Hemoglobin/Hematocrit for Epoetin Therapy

The target range for hemoglobin (hematocrit) should be Hgb 11 g/dL (33%) to Hgb 12 g/dL (36%). (**Evidence**) This target is for Epoetin therapy and is not an indication for blood transfusion therapy. (**Opinion**)

Rationale A Hgb of 11 g/dL (Hct 33%) is at the lower limit of the normal range for premenopausal females and pre-pubertal patients; a Hgb of 12 g/dL (Hct 36%) is just below the lower limit of the normal range for adult males and post-menopausal females (see Guideline 1: When to Initiate the Work-up of Anemia). Because the anemia literature in CKD patients does not distinguish between sexes, subsequent Hgb/Hct levels will apply to both males and females.

There are several pieces of evidence suggesting that patient outcomes are worse when the Hgb is ≤10 g/dL (Hct ≤30%):

1. Survival of dialysis patients declines as the Hct decreases below a range of 30% to 33%.[25,81] Survival was also shorter in dialysis patients with chronic glomerulonephritis whose mean Hgb level was 9.9 g/dL, compared to patients with polycystic kidney disease whose mean Hgb level was 11.3 g/dL.[82] Whereas one study failed to note any improved survival at a Hgb >11 g/dL compared to an Hgb 10 to 11 g/dL,[83] several other reports have shown improved survival at higher Hgb/Hct levels. Survival was improved in Italian hemodialysis patients when the Hct exceeded 32%, either spontaneously or following Epoetin therapy, when compared to Hct <32%,[84] and in the United States an Hct of 33% to 36% reduced the risk of death from any cause by 10% when compared to patients whose mean Hct was 30% to 33%.[85] Survival has been noted in one study to be better in patients with cardiac disease who attained and maintained a normal Hct compared to similar patients who did not attain and maintain a normal Hct.[80] In fact, within both the normal Hct group and the control group, the mortality decreased at higher Hct levels.[80] In those 200 patients who achieved and maintained a normal Hct for 6 months, mortality decreased to approximately 15% per year, versus 40% per year in those maintained at an Hct of 30%. There were no convincing factors that appeared to explain why those patients that did not achieve and stabilize at a normal Hct had a greater incidence of non-fatal myocardial infarctions or death than did the control group.[80]

2. Left ventricular hypertrophy (LVH) is more likely in CKD patients with anemia (Hct ≤33%)[86-88] and in patients with ESRD[89]; in such patients the risk of death is increased 2.9-fold (Endnote c).[90] Partial correction of anemia (Hgb 6.3 ± 0.8 to 11.4 ± 1.5 g/dL) with Epoetin resulted in partial regression of LVH in dialysis-dependent patients.[91] Angina was significantly decreased in patients with progressive CKD when Epoetin therapy increased the Hct to 31% ± 4% versus 23% ± 4%.[92]

3. Quality of life either is not improved, or improved only slightly, when the Hgb/Hct is increased from 8 g/dL/25% to a level no higher than 9 to 10 g/dL/28% to 30%.[93-95] However, quality of life of dialysis patients, as assessed by standardized patient questionnaires, increases as the Hgb/Hct increases above 10 to >12 g/dL and 30% to >36%.[96-98] When the results of the Amgen Phase III (mean Hct 35%) and Phase IV (mean Hct 30%) studies were compared, it was concluded that patients with Hct levels of 35% had better quality of life as measured by Karnofsky scores than those maintained at a Hct of 30%.[99] Both quality of life and various physiolog-

ical parameters in predialysis patients have been shown to be significantly better at a Hct of 36% to 39% than at 27% to 29%.[100-107]

4. In hemodialysis patients, exercise capacity (VO_2) increased when the Hct increased from 30% to 35% to 40%.[108]

5. In hemodialysis patients, the incidence of hospitalization was lower when the Hct was 33% to 36% in comparison to patients with lower Hct values.[109]

6. There are a number of studies in dialysis patients (reported initially only in abstracts) that indicate that quality of life, maximum exercise capacity, number of meters walked in 6 minutes, cardiac output, cognitive function, amino acid levels, sleep dysfunction with daytime sleepiness, insulin resistance with hyperlipidemia, and survival improved when a normal Hct was achieved,[76-78,110-118] and that there were no adverse effects observed at a normal Hct.[110,111] Several of these studies have now been published in peer review journals, and demonstrate that a normal Hgb/Hct is associated with better physical performance,[79] better cognitive function,[119] improved brain oxygen supply,[120] and improved sleep patterns[121] compared to lower Hgb/Hct levels.

Studies in patients with anemia due to conditions other than CKD also indicate that an Hct of $\leq$30% is harmful. Patients undergoing peripheral vascular surgery had more cardiac ischemia when their Hct decreased from 39% to 27% to 30% compared to others whose Hct decreased only to 32%.[122] Patients with lupus nephritis have increased mortality, unrelated to kidney dysfunction, as Hgb decreases to below 11 g/dL.[123] Patients with anemia related to cancer have improved quality of life when Hct is increased from 29% to $>$35% with Epoetin.[124] Finally, an Hgb $<$10 g/dL increases prematurity rates to almost twice normal in otherwise healthy pregnant women.[125] Since anemia is treated in these conditions to improve patient well-being and survival, patients with CKD should not be deprived of the same therapeutic goal.

Despite this plethora of data, there has been much controversy as to what Hgb/Hct is best in CKD patients. Prior to the availability of Epoetin, evidence was provided that, during neurosurgical procedures, relative oxygen transport capacity for the human brain was optimal at an Hct of 30% to 33%, as achieved by hemodilution (usually phlebotomy combined with dextran infusion).[126] This was based on in vitro hemodilution studies involving blood flow through glass capillaries.[127] This long-standing belief among anesthesiologists, neurologists, and neurosurgeons was supported by data showing that hemodilution increased cerebral blood flow. This belief has been challenged by more recent studies, which indicate that, while there is an inverse relationship between Hct and cerebral blood flow, there is a linear relationship between Hct and oxygen delivery to brain tissue, with the maximal level of oxygen delivery occurring within an Hct range of 40% to 45% (Endnote d).[128] There also was concern during the early experience with Epoetin about possible adverse effects when the Hct was increased above 30%. These adverse effects are not, in fact, seen today, except for an increase in the need for antihypertensive medications in 23% of patients with CKD, whose blood pressure can be controlled with appropriate clinical care (see Guideline 24: Possible Adverse Effects Related to Epoetin Therapy: Hypertension). Two studies of small numbers of unselected dialysis patients found no adverse effects when target Hct was increased to a mean of 38.3%[110] and 42%.[111] Hypertension was no more frequent in those cardiac patients who attained a normal Hct than patients maintained at an Hct of 30.4%.[129] In a large multicenter study of 1,200 hemodialysis patients with documented cardiac disease (congestive heart failure or ischemic heart disease), hypertension was no more frequent at a normal Hct (42% $\pm$ 3%) than at an Hct of 30% $\pm$ 3%.[80] There was no association between adverse outcomes and either (a) the average Hct during the study or (b) the Epoetin dose administered. No conclusions can be drawn from the results of this trial with regard to CKD patients who do not have heart disease (as defined in the Amgen study).

The only published investigation relating Epoetin therapy to increased cardiovascular disease is from Okinawa, Japan.[130] The authors reported that the annual incidence of stroke and acute myocardial infarction increased following the use of Epoetin in CKD patients (Endnote e). However, these findings differ from recent Euro-

pean data, in which cardiovascular morbidity and mortality were decreased by 15% to 20% after 2 years of Epoetin therapy in CKD patients.[36]

Clinicians should bear in mind that approximately 5% of hemodialysis patients attain an Hct $\geq$40%[131] without receiving Epoetin. In addition, some Epoetin-treated patients may have a spontaneous increase in Hct to above 36% after Epoetin therapy has been discontinued. There have been no published reports of an increased incidence of deaths and/or non-fatal myocardial infarctions in such patients. In view of recent abstracts[76-78,111-118] and peer-reviewed articles[79,119,120,122] showing beneficial effects from raising the Hgb/Hct to normal, it is possible that a target Hgb/Hct higher than what the Anemia Work Group recommends now may ultimately prove to be appropriate.

In summary, based on currently available data, the Anemia Work Group recommends that the Hgb/Hct be maintained between 11 and 12 g/dL (33% and 36%). In striving to maintain the Hgb/Hct within this target range, the Hgb/Hct will likely rise above this range. The reasons why some patients will temporarily exceed an Hgb/Hct of 12 g/dL (36%) is that the response to Epoetin varies amongst patients, the interplay between IV iron supplementation and epoetin dosing may be unpredictable, and it is impossible for the bell-shaped distribution of Hgb/Hct for all patients be limited to between 11 and 12 g/dL or 33% and 36%, respectively. As of January 2000, HCFA will continue to provide reimbursement for the cost of Epoetin alfa even if the Hgb/Hct temporarily rises above their target range, as long as the rolling 3-month average Hgb/Hct is $<$12.5 g/dL (37.5%). Medical justification is needed for maintaining the Hgb (Hct) above 12 g/dL (36%).

III. Iron Support

BACKGROUND

Iron is essential for hemoglobin formation, as is erythropoietin. Several important issues related to iron deficiency and its management in the CKD patient, particularly in patients receiving Epoetin therapy should be considered:

1. Iron (blood) losses are high, particularly in the hemodialysis patient.

2. Oral iron usually cannot maintain adequate iron stores, particularly in the hemodialysis patient treated with Epoetin.

3. Epoetin, by stimulating erythropoiesis to greater than normal levels, often leads to functional iron deficiency.

4. Prevention of functional (and absolute) iron deficiency by regular use of intravenous iron (ie, small doses, weekly, to replace predicted blood losses) improves erythropoiesis.

5. The serum iron, total iron binding capacity, and serum ferritin are the best indicators of iron available for erythropoiesis and iron stores, but they do not provide absolute criteria for either iron deficiency or iron overload.

These guidelines suggest that the regular use of small doses of IV iron, particularly in the hemodialysis patient, will prevent iron deficiency and promote better erythropoiesis than can oral iron therapy.

6. Prior to July 1999, the only IV iron preparation available in the United States was iron dextran. The doses recommended for iron dextran are detailed in these Guidelines. Since July 1999, iron gluconate and iron sucrose have become available for IV use in the United States. Since the amount of iron gluconate per vial differs from that of iron dextran, the Work Group recommends that the substitution of iron gluconate for iron dextran would be 8 doses of 125 mg of iron gluconate (over 8 weeks per quarter), or 8 doses of 62.5 mg of iron gluconate over 8 weeks instead of 10 doses of 50 mg of iron dextran over 10 weeks. Doses of iron gluconate larger than 125 mg given at one time are not recommended by the manufacturer, whereas iron dextran can be given at one time at doses of 250, 500, and/or 1,000 mg doses, if indicated. Iron sucrose can be given in doses of 100 mg or less.

GUIDELINE 5

Assessment of Iron Status

Iron status should be monitored by the percent transferrin saturation (TSAT) and the serum ferritin. (**Evidence**)

GUIDELINE 6

Target Iron Level

A. CKD patients should have sufficient iron to achieve and maintain an Hgb/Hct of 11 to 12 g/dL/33% to 36%. (**Evidence**)

B. To achieve and maintain this target Hgb/Hct, sufficient iron should be administered to maintain a TSAT of ≥20%, and a serum ferritin level of ≥100 ng/mL (**Evidence**).

C. In hemodialysis patients in whom TSAT is ≥20% and the serum ferritin is ≥100 ng/mL, yet the Hgb/Hct is 11 g/dL/<33%, as well as in patients requiring comparatively large doses of Epoetin to maintain an Hgb/Hct of 11 to 12 g/dL/33% to 36%, the patient's response to 1.0 g of IV iron given over 8 to 10 weeks should be observed. (**Opinion**) If in response to this course of iron, there is no increase in Hgb/Hct and no increase in serum ferritin and TSAT level, at the same dose of Epoetin, a second course of IV iron should be tried. (**Opinion**) If, in response to this second course of IV iron, there still is no increase in Hgb/Hct, but either the TSAT or serum ferritin level increases, then the weekly dose of IV iron should be reduced to the lowest amount required to maintain the TSAT ≥20% and serum ferritin at ≥100 ng/mL. (**Opinion**) If, on the other hand, in response to either of these courses of IV iron, there is an increase in Hgb/Hct at a constant dose of Epoetin, or a stable Hct at a decreased dose of Epoetin, then it is reasonable to administer 1.0 g of iron IV over 8 to 10 weeks again in an effort to achieve and maintain the Hgb/Hct at 11 to 12 g/dL/33% to 36%. (**Opinion**)

D. CKD patients are unlikely to respond with a further increase in Hgb/Hct and/or a further reduction in Epoetin dose required to maintain a given Hgb/Hct if the TSAT increases to ≥50% and/or the serum ferritin level increases to ≥800 ng/mL. (**Evidence**)

GUIDELINE 7

Monitoring Iron Status

A. During the initiation of Epoetin therapy and while increasing the Epoetin dose in order to achieve an increase in Hgb/Hct, the TSAT and the serum ferritin should be checked every month in patients not receiving intravenous iron, and at least once every 3 months in patients receiving intravenous iron, until target Hgb/Hct is reached. (**Opinion**)

B. Following attainment of the target Hgb/Hct, TSAT and serum ferritin should be determined at least once every 3 months. (**Opinion**)

C. Intravenous iron therapy, if given in amounts of 100 to 125 mg or less per week, does not need to be interrupted in order to obtain accurate measurements of iron parameters. (**Evidence**)

D. If individual doses of intravenous iron are 1,000 mg or larger, an interval of 2 weeks should occur before accurate assessment of serum iron parameters can be determined (**Evidence**). Accurate assessment of iron parameters after intravenous infusion of 200 to 500 mg of iron may require an interval of 7 or more days (**Opinion**).

E. In CKD patients not treated with Epoetin and whose TSAT is ≥20% and serum ferritin is ≥100 ng/mL, the iron status should be monitored every 3 to 6 months. (**Opinion**)

GUIDELINE 8

Administration of Supplemental Iron

A. Supplemental iron should be administered to prevent iron deficiency and to maintain adequate iron stores so that CKD patients can achieve and maintain an Hgb 11 to 12 g/dL (Hct 33% to 36%) in conjunction with Epoetin therapy. (**Evidence**)

B. If oral iron is given, it should be administered at a daily dose of at least 200 mg of elemental iron for adults and 2 to 3 mg/kg for pediatric patients. (**Evidence**)

C. The adult CKD, home hemodialysis, and peritoneal dialysis (PD) patient may not be able to maintain adequate iron status with oral iron. (**Evidence**) Therefore, 500 to 1,000 mg of iron dextran may be administered IV in a single infusion, and repeated as needed, after an initial one-time test dose of 25 mg. As of January 2000, it is not recommended to give these large doses of iron gluconate as a single infusion. (**Opinion**)

D. A trial of oral iron is acceptable in the hemodialysis patient (**Opinion**), but is unlikely to maintain the TSAT >20%, serum ferritin >100 ng/mL, and Hgb/Hct at 33% to 36%/11 to 12 g/dL. (**Evidence**)

E. To achieve and maintain an Hgb 11 to 12 g/dL (Hct of 33% to 36%), most hemodialysis patients will require intravenous iron on a regular basis. (**Evidence**)

F. Intravenous iron can be given on a variety of dosage schedules. If the TSAT is <20% and/or the serum ferritin is <100 ng/mL, the Anemia Work Group recommends that, in adults, 100 to 125 mg of iron be administered IV at every hemodialysis for 10 to 8 doses, respectively. (**Opinion**) If the TSAT remains <20% and/or the serum ferritin <100 ng/mL, another course of IV iron (100 to 125 mg per week for 10 to 8 weeks) is recommended. Once the patient's TSAT is ≥20% and the serum ferritin is ≥100 ng/mL, the Anemia Work Group recommends that 25 to 125 mg of iron be given IV once per week (see Guideline 6: Target Iron Level). (**Opinion**) Schedules for IV iron administration ranging from three times per week to once every 2 weeks are also reasonable in order to provide 250 to 1,000 mg of iron within 12 weeks. (**Opinion**)

G. Most patients will achieve an Hgb 11 to 12g/dL (Hct of 33% to 36%) with TSAT and serum ferritin levels <50% and <800 ng/mL, respectively. (**Evidence**) In patients in whom TSAT is ≥50% and/or serum ferritin is ≥800 ng/mL, IV iron should be withheld for up to 3 months, at which time the iron parameters should be re-measured before IV iron is resumed. (**Opinion**) When the TSAT and serum ferritin have fallen to ≤50% and ≤800 ng/mL, IV iron can be resumed weekly at a dose reduced by one third to one half. (**Opinion**)

H. It is anticipated that once optimal Hgb/Hct and iron stores are achieved, the required maintenance dose of IV iron may vary from 25 to 125 mg/week for hemodialysis patients. The goal is to provide a weekly dose of IV iron in hemodialysis patients that will allow the patient to maintain the target Hgb/Hct at a safe and stable iron level. The maintenance iron status should be monitored by measuring the TSAT and serum ferritin no less than every 3 months. (**Opinion**)

I. Oral iron is not indicated for the CKD

patient who requires maintenance doses of IV iron. (**Opinion**)

RATIONALE FOR GUIDELINES 5-8

Background

Effective erythropoiesis requires both iron and erythropoietin. When CKD patients lack an adequate supply of either one or both, anemia results. Among United States ESRD patients receiving Epoetin, more than 50% are iron deficient, which probably accounts, at least in part, for why the mean Hct among ESRD patients in the United States in 1993 was 30.2%, with 43% having a Hct <30% (Endnote f).[66] To remedy this problem, clinicians will need to address three important issues regarding management of iron in CKD patients:

1. Under what circumstances should a patient receive supplemental iron?
2. How much iron should they receive?
3. How (by what route and according to what dosing schedule) should they receive it?

The Iron Support section of these guidelines (Guidelines 5-10) addresses how to ensure that patients have sufficient iron to achieve and maintain a target Hgb 11 to 12 g/dL (Hct of 33% to 36%). The Administration of Epoetin section (Guidelines 11-19) addresses how to ensure that patients receive sufficient Epoetin to achieve and maintain a target Hgb 11 to 12 g/dL (Hct of 33% to 36%).

In formulating its recommendations regarding these issues, the Anemia Work Group focused on the following:

1. The iron needs and the importance of maintaining adequate iron status in CKD patients
2. Assessment of iron status: the sensitivity and specificity of the TSAT and serum ferritin in detecting absolute and functional iron deficiency, as well as iron overload
3. An analysis of the effectiveness of oral versus IV iron
4. Administration of IV iron, and its potential associated risks
5. Iron overload

Iron Needs in CKD Patients

Iron deficiency is common in CKD, particularly in hemodialysis patients, for several reasons, including substantial losses of blood from frequent blood tests, blood remaining in the dialysis tubing and dialyzer, and gastrointestinal blood losses, that cannot be compensated for by sufficient absorption of iron from the gastrointestinal tract. Epoetin therapy increases the rate of erythropoiesis and therefore the demand for iron, which, when coupled with substantial blood losses, compounds the difficulty of maintaining adequate iron stores in hemodialysis patients.

Normal body iron stores are 800 to 1,200 mg.[132] If the initial Hct is 25% and the target Hct is 35%, the magnitude of supplemental iron required by patients during the first 3 months of Epoetin therapy is approximately 1,000 mg. Of this, approximately 400 mg of iron are needed simply to replace iron losses during 3 months of hemodialysis (Endnote g). The other 600 mg of iron are needed to support production of sufficient numbers of red blood cells to achieve the target Hgb/Hct (Endnote h). Once the target Hgb/Hct is achieved, approximately 400 to 500 mg of supplemental iron will be needed every 3 months to replace iron losses and maintain adequate iron stores.

In children, mean daily intestinal blood losses (pre-dialysis) are 6 mL/m^2 BSA. For pediatric hemodialysis patients, mean daily GI blood losses increase to 11 mL/m^2, and dialysis-associated blood losses are 8 mL/m^2 per treatment. Cumulative annual iron losses therefore approximate 1.6 g/1.73 m^2 in pediatric hemodialysis patients, and 0.9 gm/1.73 m^2 in predialysis pediatric patients and probably in those on PD.[133] Although there are no data on the calculated iron needs in pediatric patients on dialysis, the rationale for iron supplementation is similar to that described for adults.

Assessment of Iron Status

An ideal test of a CKD patient's iron status would accurately indicate whether the patient has:

1. Sufficient amount of iron available to support achievement and maintenance of an Hgb 11 to 12 g/dL (Hct of 33% to 36%); and
2. An excessive amount of body iron.

Unfortunately, no test exists which accomplishes either of these goals and which is practical to administer (Endnote i).

Currently, the two best tests of iron status are the percent TSAT and the serum ferritin. The

percent TSAT (serum iron multiplied by 100 and divided by total iron binding capacity [TIBC]) reflects iron that is readily available for erythropoiesis. The TIBC essentially measures circulating transferrin. The transferrin molecule contains two binding sites for transporting iron from iron storage sites to erythroid progenitor cells. A TSAT of 50% indicates that half of the binding sites are occupied by iron. Normally there is a diurnal variation in the level of serum iron and, thus, the TSAT. Since blood for these tests is generally obtained at the same time of day in relation to either clinic or dialysis visits, serial measurements of TSAT typically are not affected by this diurnal variation.

The distinction between absolute and functional iron deficiency is crucial to understanding what constitutes adequate TSAT and serum ferritin levels in Epoetin-treated patients. In otherwise healthy subjects, iron deficiency is considered "absolute" when iron stores are depleted, as indicated by serum ferritin levels $<$12 ng/mL,[54] and iron delivery to the erythroid marrow is impaired, as evidenced by TSAT levels below 16%.[53] Absolute iron deficiency in CKD patients has been defined as serum ferritin levels $<$100 ng/mL and TSAT levels $<$20%. In contrast to absolute iron deficiency, functional iron deficiency results when there is a need for a greater amount of iron to support hemoglobin synthesis than can be released from iron stores (reticuloendothelial cells). This situation, which can be caused by pharmacological stimulation of erythropoiesis by Epoetin, can occur in the presence of adequate iron stores. As a result, the percent TSAT decreases to levels consistent with iron deficiency despite a normal or elevated serum ferritin.[35,134-136] Patients with this condition do not meet traditional laboratory criteria for absolute iron deficiency, but may demonstrate an increase in Hgb/Hct when IV iron is administered.

A common clinical problem is distinguishing between functional iron deficiency and an inflammatory iron block, since the TSAT may be $<$20% and serum ferritin may be 100 to 700 ng/mL in both situations (although the serum ferritin can be even higher in the presence of inflammation). In the former condition, serial levels of serum ferritin decrease during Epoetin therapy, yet remain elevated ($>$100 ng/mL); in contrast, in the latter condition, there is usually an abrupt increase in serum ferritin associated with a sudden drop in the TSAT. If it is not clear which of these conditions exists, it is recommended that weekly IV iron (50 to 125 mg) be given for up to 8 to 10 doses. If no erythropoietic response occurs, an inflammatory block is most likely, and no further IV iron should be given until the inflammatory condition has resolved.

Transferrin Saturation Traditionally, a TSAT of $<$20% in hemodialysis patients has been considered to be indicative of iron deficiency. However, several studies[52,137-143] have demonstrated that a TSAT of $<$20% versus $\geq$20% is not an accurate discriminator between patients who are or are not iron deficient. Although the vast majority of patients who have a TSAT $<$20% are iron deficient, there are some patients who have a TSAT $<$20% who are able to achieve a Hct of 33% to 36% and/or do not respond to higher doses of iron (and TSAT levels) with either an increase in Hct or maintenance of Hct with a reduced dose of Epoetin. However, there also are many patients who have a TSAT $>$20% who are functionally iron deficient (ie, they respond to higher doses of iron, and a corresponding increase in their TSAT, with either an increase in their Hct or maintenance of their Hct at a reduced dose of Epoetin)[52,137-143] (Endnote j).

Ferritin Whereas TSAT reflects iron that is readily available for erythropoiesis, serum ferritin reflects storage iron, ie, iron that is stored in liver, spleen, and bone marrow reticuloendothelial cells. As is the case with the TSAT, the serum ferritin level is most accurate as a predictor of iron deficiency or iron overload when it is extremely low or extremely high, respectively.

Just as serum ferritin is not perfectly sensitive, it also is not perfectly specific. In part, this is due to the fact that, in addition to reflecting body iron stores, serum ferritin also is an acute phase reactant. As such, it can increase in the setting of either acute or chronic inflammation.

While no single value of TSAT or serum ferritin accurately discriminates between CKD patients who are or are not functionally iron deficient, available data demonstrate that the lower the TSAT and the serum ferritin, the higher the likelihood that a patient is iron deficient, and

the higher the TSAT and the serum ferritin, the lower the likelihood that a patient is iron deficient.[139-146]

Other tests of iron status, such as zinc protoporphyrin or RBC ferritin, are less widely available and appear to offer no increase in diagnostic sensitivity or specificity over serum ferritin and TSAT.[147] The percent of hypochromic red blood cells does appear to be a sensitive and reliable indicator for iron deficiency and has been shown to be helpful in the diagnosis of functional iron deficiency.[55,56] Normally, there are less than 2.5% of red blood cells with individual cell hemoglobin levels of less than 28 g/dL. Values exceeding 10% are compatible with iron deficiency in the Epoetin-treated patient. This measurement is presently performed as part of a routine full blood count sample that requires a Technicon H-1, H-2, or H-3 automated cell counter, which is specialized equipment (Bayer Diagnostics) available in parts of Europe, but is presently not available in most medical centers in the United States.

Several recommendations of a European Erythropoietin Symposium regarding iron supplementation (whether oral or IV) during Epoetin therapy were as follows:

1. Serum ferritin should be maintained at greater than 100 ng/mL. No upper limit was set.
2. Transferrin saturation should be maintained at greater than 20%. Hypochromic red blood cells should be maintained at less than 10%. Iron status should be evaluated monthly initially, then every 2 to 3 months.[148]

Use of Oral Versus Intravenous Iron

Inadequacy of Oral Iron in Hemodialysis Patients A number of studies have documented the failure of oral iron supplements to maintain adequate iron stores in Epoetin-treated hemodialysis patients[52,134,135,139,141,149-153] (Table IV-2). Even though there may be temporary improvement in the Hct with oral iron therapy, blood (iron) losses exceed the absorption of iron from oral supplements in most Epoetin-treated hemodialysis patients and ultimately iron stores decrease (as indicated by decreasing serum ferritin levels; Table IV-2). Eventually, as negative iron balance continues, iron stores decrease and will become inadequate.

Although there is no evidence to suggest that gastrointestinal iron absorption is impaired in patients with kidney failure,[154-156] even in non-CKD individuals only a small fraction of oral iron is absorbed. Consequently, 200 mg of elemental iron ingested daily usually cannot meet the demands of Epoetin-induced increase in erythropoiesis and hemodialysis-associated blood losses. Moreover, since oral iron absorption is inversely correlated with body iron stores, it is unlikely that even a greater amount of oral iron would be absorbed when the serum ferritin level exceeds approximately 200 ng/mL[155,157] or the transferrin saturation exceeds 20%[158] levels that are needed for optimal erythropoiesis. On the other hand, iron absorption also correlates with the degree of erythropoiesis, and can be increased during Epoetin therapy.[159,160] However, in the latter study involving normal subjects,[160] enhanced erythropoiesis was achieved with amounts of Epoetin greater than those generally given to patients with CKD.

Inadequate absorption of oral iron is exacerbated by the fact that patient compliance with oral iron regimens is often poor due to one or

Table IV-2. Effects of Oral Iron Therapy in Hemodialysis Patients

Study	No. of Patients	Elemental Iron/Day	Duration (mo)	Baseline/Follow-Up Hgb/Hct	%TSAT	Ferritin	Epoetin Dose
Kooistra et al[151]	19	105	10	22.8-32.8	25-24	447-265	75 U/Kg/wk
Dunea et al[152]	73	260	12				2-4,000 U/HD
	50			27.0-33.7	NA	123-83	
	23			29.6-27.5	NA	99-126	
Bergmann et al[149]	7	227	5	22.0-29.0	NA	400-100	360 U/kg/wk
Macdougall et al[141]	13	120	4	7.2-10.0	27-31	309-100	75 U/kg/wk
Wingard et al[150]	46	200	6	26.3-29.7	20-21	151-106	10,660 U/HD
Anastassiades et al[153]	38	300	3	6.9-10.4	29-27	211-92	110 U/kg/wk
Fishbane et al[139]	32	195	4	31.8-31.8	21-20	179-157	7563 U/HD
Horl et al[135]	12	40-80	3	22.5-33.0	NA	1,145-251	150 U/Kg/wk

more of the following: the inconvenience of dosing (1 hour pre-prandial or 2 hours post-prandial administration for optimal absorption); side effects, including gastric irritation and constipation; and out-of-pocket cost.

Although most Epoetin-treated hemodialysis patients will require intravenous iron to maintain iron stores, a small percentage of hemodialysis patients, as well as many peritoneal dialysis and CKD patients, are able to maintain adequate iron stores using only oral iron supplements, perhaps as a result of augmented intestinal iron absorption,[160] smaller blood losses, and/or lower Epoetin requirements.[52,140]

IV Iron Intravenous iron has been shown to improve responsiveness to Epoetin in selected patients with CKD and PD patients[52,140,161] and may reduce the amount of Epoetin needed (if used) to achieve and maintain a target Hgb/Hct. In addition, frequent administration of low doses of IV iron improves the Hgb/Hct and can reduce Epoetin requirements in hemodialysis patients (Table IV-3)[139-142,144-146,162] (Endnote k). In addition, several studies have shown that even without the use of Epoetin, the Hgb/Hct can increase in a significant number of patients treated with frequent doses of IV iron, but not always to the target level[52,134,140] (Table IV-3). Several studies have shown the superiority of IV iron therapy by comparing it to oral iron therapy and showing that IV iron therapy either increases the Hgb/Hct and/or reduces Epoetin requirements.[139,141,163] In the 8 studies, reported by 7 authors, in which iron stores were thought to be normal based upon a serum ferritin of >100 ng/mL (in 5 of these studies, the baseline TSAT values were 23% to 31%), the response to a prorated weekly dose of IV iron ranging from 30 to 200 mg resulted in an increase in Hgb/Hct of 19% ± 20% and a reduction in Epoetin requirements of 34% ± 27%.[139-142,144,146,161,162] Other studies have shown the erythropoietic benefit of increasing the TSAT to >20% and serum ferritin to >100 ng/mL, respectively.[138,143]

IV Iron Protocol

The protocol that the Anemia Work Group recommends for administering IV iron dextran or iron gluconate in adult hemodialysis patients with absolute iron deficiency is 100 mg of iron dextran or 125 mg of iron gluconate during each dialysis for 10 or 8 doses respectively. For maintenance iron therapy, and treatment and prevention of functional iron deficiency, the recommen-

Table IV-3. Effects of Intravenous Iron Therapy in Hemodialysis Patients

Study	No. of Patients	IV Iron (mg/wk)	Duration (mo)	Baseline/Follow-Up			Changes	
				Hgb/Hct	%TSAT	Ferritin	Hgb/Hct	Epoetin
Effect in Iron Deficiency								
Sunder-Plassmann and Horl[145]	52	100	6	9.4-11.1	13-24	52-534	+18%	−17%
Taylor et al[144]	12	31	6	10.1-11.0	NA	68-211	+09	−33%
Sepandj et al[146]	50	50	6	8.8-10.0	NA	36-217	+14%	−34%
Effect with "Normal" Iron Stores								
Silverberg et al[140]	41	50	6	28.7-33.7	27-31	99-403	+17%	0
Senger and Weiss[162]	13	25-50	12	32.6-34.7	14-36	111-609	+06	−75%
Taylor et al[144]	34	31	6	9.9-11.3	NA	176-305	+14	−33%
Fishbane et al[139]	20	200	4	32.5-34.4	23-75	191-754	+12	−46%
Granolleras et al[142]	18	30	4	29.0-31.0	31-33	321-654	+07	−30%
Silverberg et al[140]	41	50	6	33.7-33.6	31-29	403-383	0	−61%
Macdougall et al[141]	12	125	4	7.3-11.9	26-23	345-350	+63	0
Suh and Wadhwa[161]	7*	100	7	29.0-38.0	18-35	267-660	+31	−27%
Effect without Epoetin								
Allegra et al[134]	11	93	6	7.0-8.0	NA	60-500	5/11 pts responded	
	7	93	6	7.0-7.0	NA	700-900	0/7 pts responded	
Silverberg et al[140]	5*	50	6	27.7-35.6	24-36	145-460	+17%	
Silverberg et al[52]	33†	50	5	29.6-31.5	22-27	106-297	66%	

* CAPD patients.
† CKD patients.

dation is 25 to 100 mg of IV iron dextran every week for 10 weeks, or 31.25 to 125 mg of iron gluconate every week for 8 weeks, with measurement of the TSAT and serum ferritin no sooner than 2 to 7 days after the last dose, depending on the magnitude of the above doses. Doses of 100 to 125 mg require 7 days to elapse for accurate monitoring.[164-168] Measurement of transferrin saturation and serum ferritin may be inaccurate if they are performed within 14 days of receiving a single dose of 1 gram or more of iron intravenously.[143,168,169]

The frequency of maintenance IV iron therapy can be thrice weekly (with every hemodialysis),[142] twice weekly,[139,144] weekly,[140,145,161,162] or every other week,[141] but should provide 250 to 1,000 mg of iron within 12 weeks. Iron status during the maintenance phase of Epoetin treatment should be monitored by measuring the TSAT and serum ferritin every 3 months.

Dosing of IV iron in pediatric patients should be adjusted to weight. The regimen employed successfully for a 10-dose course of IV iron in one study for pediatric hemodialysis patients is shown in Table IV-4.[170] The dosing recommendations for pediatric CKD and PD patients are shown in Table IV-5.

There have been no studies of the maintenance use of IV iron in pediatric patients. There is no rationale for prescribing oral iron supplements, given their inconvenience, cost, and side effects, when IV iron is required.

Another recommendation of the European Erythropoetin Symposium regarding iron supplementation during Epoetin therapy was as follows: IV iron is preferable for hemodialysis patients and may also be appropriate for some patients on CAPD and for some CKD patients not on dialysis.[148]

The rationale for recommending regular amounts of IV iron therapy to patients receiving Epoetin for treatment of anemia of CKD is that:

Table IV-4. Iron Dextran Dosing Recommendations for Pediatric Hemodialysis Patients

	Patient Weight		
	<10 kg	10 to 20 kg	>20 kg
Each dose of a 10-dose course	0.5 mL (25 mg)	1.0 mL (50 mg)	2.0 mL (100 mg)

Table IV-5. Iron Dextran Dosing Recommendations for Pediatric Predialysis and PD Patients

	Patient Weight		
	<10 kg	10 to 20 kg	>20 kg
Iron dose	125 mg	250 mg	500 mg
Volume of saline for infusion	75 mL	125 mL	250 mL

1. Erythropoiesis requires both iron and erythropoietin.

2. Oral iron fails to maintain adequate iron stores in most hemodialysis patients, resulting in persistence of moderate anemia, which increases morbidity and mortality.

3. The use of IV iron will increase Hgb/Hct, and therefore improve morbidity and survival in CKD patients.

4. The health benefits of IV iron are expected to exceed its adverse effects (see Guideline 9: Administration of a Test Dose of IV Iron Dextran), resulting in a net health benefit.

The Use of Intravenous Iron Preparations

There are two iron dextran preparations available for IV use in the United States, INFeD® and Dexferrum®, both of which are clinically effective. In 1999 the intravenous iron preparation, ferric sodium gluconate, Ferrlecit®, and in 2000 iron sucrose were approved for use by the Food and Drug Administration. Ferric sodium gluconate and iron sucrose have had extensive use in Europe and other countries and there is literature regarding their safety and efficacy.[134,140,144,145,166,167,171-175] Intravenous iron dextran may cause dose-related arthralgias and myalgias, as well as idiosyncratic reactions (anaphylactic-like, hypotension) that are not dose-related (see Guideline 9: Administration of a Test Dose of IV Iron Dextran). Dose-related adverse effects occur infrequently and are generally mild when doses of ≤100 mg are used.[176,177] It is therefore recommended that in-center hemodialysis patients be given no more than 100 mg per dose of iron dextran IV to minimize the dose-related arthralgias/myalgias. The use of frequent, small doses of iron dextran, given as an IV "push" over 2 minutes, is also more economical than giving larger boluses administered as an intravenous infusion in dextrose in water or saline.[178] However, it is not realistic

to expect a CKD, home hemodialysis, or PD patient to come to a clinic for 10 consecutive weeks to receive a cumulative iron dose of 1,000 mg in 100 mg increments. Therefore, for CKD, home hemodialysis, and PD patients who, despite oral iron supplementation, have developed evidence of iron deficiency, it is reasonable to administer IV iron dextran (in the clinic or dialysis center) in single doses of 500 to 1,000 mg diluted in 250 mL of normal saline and infused over 1 hour, and repeated as often as necessary to maintain adequate iron stores. Patients should be informed of the increased incidence of myalgias/arthralgias associated with such doses.

Intravenous ferric sodium gluconate is now available in 62.5 mg/5.0 mL ampules. This form of IV iron has been claimed to cause "oversaturation" of transferrin, leading to hypotension, caused by free iron.[167] However, it is now known that the term "oversaturation" may be an artifact, depending on how serum iron is measured in the clinical laboratory. One method used in the United States utilizes an acetate buffer with hydroxylamine hydrochloride, which mainly measures iron bound to transferrin (true bioavailable serum iron). However, a method that uses a buffer with ascorbic acid and guanidine, releases more iron from recently administered IV iron compounds, thus artifically raising the serum iron level, and contributing to possible "oversaturation" of transferrin, thus overestimating availability of "free iron."[179] If the ascorbic acid/guanidine buffer method is utilized, infusion of 62.5 mg over the course of 4 hours of dialysis will avoid this artifact, whereas the infusion of the same amount over 30 minutes and the infusion of 125 mg over 4 hours may result in transient "oversaturation" of transferrin.[167] However, few adverse effects were reported when 62.5 mg and 125 mg doses of iron gluconate were mixed in 50 or 100 mL of saline, respectively, and infused over 30 or 60 minutes.[165] Clinical trials are now in progress to determine whether bolus infusions of these amounts of iron gluconate over 5 to 10 minutes are safe. However, the infusion of more than 125 mg of iron gluconate as a bolus or infusion is not recommended at this time by the manufacturer. Therefore, the way in which intravenous iron is administered should depend upon the form of iron preparation that is used and the amount. Also, shortly after the IV administration of iron preparations, spuriously high transferrin saturation levels may occur due to the measurement of circulating drug iron.

Possible Adverse Effects Related to Intravenous Iron Preparations The safety of IV iron dextran, iron gluconate, and iron sucrose must be considered before recommending their routine use in adult or pediatric patients as part of the overall approach to the management of anemia of CKD. There are very few large-scale studies that have examined the incidence of adverse effects associated with these preparations.[180] The incidence of life-threatening/serious acute reactions to IV iron dextran has been reported to be 0.65% (3 of 471 general patients)[176] and 0.7% (4 of 573 dialysis patients).[181] Because patients may have a serious adverse reaction to IV iron dextran after having received IV iron dextran without incident in the past, and because patients who have a serious adverse reaction to IV iron dextran tend not to receive IV iron dextran again, the rate of serious or potentially life-threatening adverse reactions to IV iron dextran, as a proportion of injections, rather than patients, is even smaller—approximately 0.1%.[176] Although this incidence is low, it suggests that 1,200 life threatening/serious acute reactions could occur in the 200,000 hemodialysis patients in the United States if all received IV iron dextran. Some data are based on patients who received iron dextran formerly sold as Imferon®,[176] which is no longer produced in the United States, and InFeD®,[181] whose molecular weight is 96,000. Most of the reported adverse events were related to the use of Imferon. It is not clear whether the incidence of side effects from InFeD® is identical to that from Imferon®.[182] Another intravenous iron dextran preparation, DexFerrum® has a molecular weight of 265,000.[168,180] There are no published data documenting the incidence of adverse events with the use of DexFerrum®. Prospective information needed to compare reaction rates between these two agents (InFeD® and DexFerrum®) is lacking. In the absence of information on mechanism of reaction, patients who have shown severe reactions to either agent should not be administered the other.

Delayed reactions to IV iron dextran, characterized by arthralgias and myalgias, are dose-

related and rarely occur with doses of 100 mg or less.[176] By contrast, as many as 59% of patients experience the arthralgia-myalgia syndrome after total dose infusion (TDI).[183-186] Occurrence of an arthralgia-myalgia reaction should prompt a decrease in the dose of IV iron dextran administered. Low dose administration, however, may require more frequent dosing to maintain optimum iron status. Although arthralgias and myalgias have been reported with iron gluconate, these are acute, rather than delayed, and are likely attributable to the same mechanism as the arthralgias and myalgias associated with iron dextran. The relationship of arthralgias and myalgias to the rate of administered dose or total dose of iron gluconate has not been examined.

Use of ferric sodium gluconate (Ferrlecit®) may rarely be associated with hypotension and flushing, loin pain and intense upper gastric pain, the latter without hypotension.[175] A subsequent report from the same institution regarding the same iron preparation claimed that there were no immediate or delayed adverse effects, when 62.5 mg was diluted in 50 mL of saline and given over 30 minutes.[172] Another report describes a study in which ferric gluconate was administered to three patients who were also receiving an ACE inhibitor. These patients all had iron deficiency and had normal renal function. One patient received 120 mg of ferric gluconate daily and, after the fourth infusion, developed abdominal cramps and hypotension.[176] Two other patients received 62.5 mg of ferric gluconate and developed abdominal cramps, diarrhea, and hypotension 1 hour after the end of a slow infusion of the compound. It is not clear whether the use of an ACE inhibitor was a factor in these reactions. Reactions to iron gluconate are somewhat less common than to iron dextran, and of lesser severity. There have been no reported deaths due to the IV use of iron gluconate.[180] In the hemodialysis patients participating in one of the first US trials with sodium gluconate,there is no evidence that patients who react to iron dextran will react to iron gluconate.[165]

Iron sucrose (Venofer) has completed clinical trials in the United States, and is used extensively in Europe and Israel. The FDA approved this drug in November 2000. It is available in 100 mg (5 mL) vials. One report[166] noted that if transferrin levels were less than 180 mg/dL, free iron might occur if 100 mg of iron saccharate were administered. The administration of doses of 10, 20, or 40 mg of iron saccharate did not result in free iron.

Since there are so little data published concerning the possible adverse effects of IV iron preparations, the Anemia Work Group recommends the establishment of a registry for monitoring the incidence of severe, acute, adverse reactions to IV iron in CKD patients. Such a registry should be designed by a committee of clinical, scientific, and methodological experts, maintained by parties, such as NKF-K/DOQI, without an economic interest in parenteral iron or Epoetin therapy, and used to provide periodic, published reports.

Iron Overload

There is little information in the literature which clearly establishes the upper limit of safety for serum ferritin in patients receiving IV iron therapy. For instance, iron overload has been defined as being present when the serum ferritin chronically remains above 1,000 ng/mL[154] or above 500 ng/mL[153] by the same authors. On the other hand, a study in which bone marrow iron stores were assessed in conjunction with serum ferritin levels in Epoetin-treated dialysis patients indicated that iron overload was not present in conjunction with a serum ferritin level as high as $1,047 \pm 445$.[183] While accumulation of iron in tissues such as the heart, liver, and pancreas (as seen in primary hemochromatosis) can be hazardous, most of the iron accumulation from iron overload in dialysis patients is in the reticuloendothelial cells,[169] with very little parenchymal cell damage.[187] Iron deposition in proximal muscle was demonstrated in 10 iron overloaded hemodialysis patients, whose serum ferritin levels were 1,030 to 5,000 ng/mL.[188] However, these patients inherited the hemochromatosis alleles. Liver cell damage was noted in the pre-Epoetin era when some adult and pediatric dialysis patients developed transfusional hemosiderosis and had serum ferritin levels in excess of 7,500 ng/mL and TSAT levels greater than 88%[189,190] (Endnote l). However, it is difficult to separate the effect of hepatitis B or C, which commonly occurred in this setting, from the effect of iron overload per se.

Transferrin, which is present in plasma and lymph, normally is not more than 50% saturated with iron. In this setting, there is no free iron available for cell growth of microorganisms.[191] An increased incidence of bacterial infections has been reported to be associated with iron overload.[192-194] However, there is a dichotomy between the in vitro and in vivo data as to whether iron suppresses phagocytosis[192,195,196] and whether iron overload induces infection.[197] It is known that anemia is associated with an increased incidence of infection, that idiopathic hemochromatosis is not associated with an increased incidence of infection and that patients with thalassemia who receive multiple transfusions and develop hemosiderosis only develop an increased incidence of infections if they have had a splenectomy.[197] Furthermore, it is difficult to differentiate between the immunological suppression that results from multiple transfusions and any effect of iron overload per se in causing bacterial infections (Endnote m). A more recent study by authors who had earlier noted an increased incidence of infection in association with high serum ferritin levels (Endnote m)[194] in anemic hemodialysis patients prior to the advent of Epoetin therapy re-examined this issue and found that anemia (Hgb $\leq$9 gm/dL), and not an elevated serum ferritin level, is a risk factor for an increased incidence of bacteremia.[198] The polymorphonuclear granulocyte dysfunction that may be present in iron-overloaded dialysis patients has been shown to normalize following either desferoximine or Epoetin therapy with serum ferritin levels still remaining greater than 1,000 ng/mL.[199,200] On the other hand, neutrophil dysfunction has also been noted in hemodialysis patients who are not iron overloaded, but who are receiving IV iron, with transferrin saturation values $<$20% associated with serum ferritin levels $>$650 ng/mL.[201] Whether this dysfunction occurred because of associated inflammatory state or was related to functional iron deficiency is not clear. Moreover, since serum ferritin is an acute phase reactant, infection may increase the serum ferritin level into a range consistent with iron overload. In such circumstances, the association between an increased ferritin level and an increased incidence of infections is due to infection resulting in an increased ferritin level, rather than iron overload resulting in an increased risk of infection.

After reviewing this literature, the Anemia Work Group concluded that maintaining a serum ferritin level within the range recommended in these guidelines is unlikely to expose the patient with CKD to an increased risk of bacterial infections. Furthermore, in hemodialysis patients, because of repetitive dialyzer blood losses, serum ferritin levels will decline by withholding IV iron, as noted in two studies where the serum ferritin levels decreased from 754 $\pm$ 34 ng/mL and 836 $\pm$ 393 ng/mL to 183 $\pm$ 18 ng/mL and 477 $\pm$ 267 ng/mL, respectively, within 4 and 3 months.[166,181] Furthermore, iron overload, if present, can be reduced by the combination of increased Epoetin therapy and regular phlebotomy.[202]

Summary

Available evidence demonstrates that:

1. Both iron and erythropoietin are needed to produce red blood cells; as a result, unless adequate iron is available, Epoetin will be relatively ineffective.

2. In the absence of provision of supplemental iron, iron deficiency is almost always present in nontransfused hemodialysis patients receiving Epoetin.

3. Although some hemodialysis patients have been able to avoid absolute and functional iron deficiency by taking only oral iron supplements, most hemodialysis patients require IV iron to maintain sufficient iron to achieve and maintain an Hgb (Hct) of 11 to 12 g/dL (33% to 36%).

4. Just as there is risk associated with the failure to use IV iron (because many patients will be anemic unless they receive IV iron, and anemia is associated with increased morbidity and mortality), there also is some risk associated with the use of IV iron dextran and ferric sodium gluconate (see Guideline 9: Administration of a Test Dose of IV Iron Dextran).

5. Although no tests are perfect indicators of the adequacy of iron stores, the TSAT and serum ferritin are the best measures of the body's iron status that we currently have. The probability that iron deficiency is present increases as the values of these measures decrease.

6. Given the prevalence of iron deficiency in CKD patients, and the sensitivity and specificity

of TSAT and serum ferritin in detection of iron deficiency, the likelihood of iron deficiency is sufficiently high when TSAT is <20% and the serum ferritin is <100 ng/mL. Therefore, the TSAT and serum ferritin should be maintained at a level of ≥20% and ≥100 ng/mL, respectively, in all patients.

7. Because many patients will still be functionally iron deficient even with a TSAT ≥20%, and/or serum ferritin ≥100 ng/mL, additional iron should be given to patients whose TSAT is ≥20% and/or serum ferritin is ≥100 ng/mL, whenever the Hct is <33% and/or Epoetin doses are greater than anticipated, so long as administration of such iron does not chronically maintain the TSAT at >50% or serum ferritin at >800 ng/mL. There is no single level of TSAT or serum ferritin that is optimal for all patients. The goal of iron therapy is to improve erythropoiesis, not to attain specific levels of TSAT and/or serum ferritin.[203] The probability that functional iron deficiency exists despite a TSAT ≥20% is greater in patients who require higher doses of Epoetin.

8. The levels of TSAT or serum ferritin above which patients will have iron overload is not known. Patients with transfusional hemosiderosis have a TSAT ≥80%.[190] There is no known risk associated with a TSAT that is ≤50%. Conversely, there is no physiologic or clinical rationale for maintaining TSAT >50%. Serum ferritin levels between 300 and 800 ng/mL have been common in dialysis patients, and there has been no evidence that such levels are associated with adverse, iron-mediated effects.

9. Because of the repetitive dialyzer-related blood losses in hemodialysis patients, iron overload can be avoided by temporarily withholding IV iron administration if TSAT or ferritin levels temporarily become too high.

10. By monitoring the TSAT and serum ferritin at least once every 3 months, erythropoiesis can be optimized in hemodialysis patients by adjusting the pro-rated weekly dose of IV iron to maintain adequate iron status.

GUIDELINE 9

Administration of a Test Dose of IV Iron

Prior to initiating IV iron dextran therapy, a one-time test dose of 25 mg (in adults) should be given IV. For pediatric patients weighing <10 kg, the test dose should be 10 mg; for pediatric patients weighing 10 to 20 kg, the test dose should be 15 mg. If no immediate allergic reaction occurs, subsequent routine doses can be given without a test dose. According to the package insert, iron dextran should be administered by slow IV push at a rate not to exceed 1.0 mL (50 mg, if undiluted) per minute. (**Opinion**)

Prior to initiating IV iron gluconate therapy in adults, a one-time test dose of 25 mg should be given IV. If no immediate allergic reactions occurs, subsequent routine doses can be given without a test dose. According to the package insert, the test dose should be diluted in 50 mL 0.9% sodium chloride for injection and administered over 60 minutes. Also, according to the package insert, iron gluconate has not been established to be safe and effective in pediatric patients.

Rationale Acute adverse reactions may be seen with administration of IV iron dextran and IV iron gluconate. In addition, delayed reactions may be seen with the use of IV iron dextran. Severe acute reactions resembling anaphylaxis with dyspnea, hypotension, chest pain, angioedema or urticaria are uncommon. Anaphylaxis-like reactions occur in fewer than 1% of iron dextran or iron gluconate administrations. Fatalities associated with the use of iron dextran are rare[176,181] and have not been reported in association with the use of iron gluconate.[175] A history of multiple drug allergies is associated with increased risk of an acute iron dextran reaction,[176] but a similar association has not been reported for iron gluconate. Anaphylaxis-like reactions to iron dextran usually occur within a few minutes after injection and typically respond readily to treatment with IV epinephrine, diphenhydramine, and corticosteroids. It is common practice to wait 15 to 60 minutes after the initial test dose before the remainder of the initial therapeutic dose is injected, assuming no initial anaphylaxis-like reaction occurred. *It is recommended that the test dose and subsequent doses of iron dextran, iron gluconate, or iron sucrose be administered by personnel trained to provide emergency treatment and that there be immediate access to the medications needed for the treatment in the rare case of a serious allergic reaction.*

Table IV-6. Amount of Elemental Iron and Cost of Various Oral Iron Preparations[208]

Iron Preperation (without added vitamins or folic acid)	Tablet Size (mg)	Amount of Elemental Iron (mg)	Average Monthly Wholesale Cost (200 mg/day*)
Ferrous gluconate	325	35	$5.08
Ferrous sulfate	325	65	$2.29
Ferrous fumarate	325	108	$1.63
Polysaccharide-iron complex		150	$7.12†

* Of elemental iron.
† 150 mg iron per day.

Test doses for iron dextran and iron gluconate are not interchangeable. An uneventful response to either agent does not preclude an adverse reaction to the other or to repeat administration of the same agent. It should be noted that a test dose for either iron dextran or iron gluconate has limited value. There is no evidence that acute, anaphylaxis-like reactions to iron dextran or iron gluconate are less severe after a 25 mg test dose than after a therapeutic 100 or 125 mg dose. For iron dextran, most patients who suffer severe acute reactions have successfully received both a test dose and multiple therapeutic doses in the past. For iron gluconate it is likely that the same phenomenon will be observed, although data on this point are not currently available. Thus, the test dose neither minimizes reaction to a first dose nor prospectively identifies the patient at increased risk for a severe reaction to a later dose. Caution is warranted with every dose of iron dextran that is administered.

GUIDELINE 10

Oral Iron Therapy

When oral iron is used, it should be given as 200 mg of elemental iron per day, in 2 to 3 divided doses in the adult patient, and 2 to 3 mg/kg/day in the pediatric patient. Oral iron is best absorbed when ingested without food or other medications. (**Evidence**)

Rationale In CKD and PD patients with minimal daily iron losses, provision of 200 mg elemental oral iron per day may be sufficient to replace ongoing losses and support erythropoiesis. Intestinal absorption of iron is inversely related to iron stores.[155,156] Iron absorption is also increased as erythropoiesis increases, such as occurs with Epoetin therapy.[150,159,160] While studies in the pre-Epoetin era indicated that iron absorption was minimal with serum ferritin levels above 100 ng/mL and TSAT values above 20%, the amount of iron absorbed in CKD patients in the presence of Epoetin therapy remains poorly documented. One study indicated minimal absorption if the serum ferritin was greater than 100 ng/mL.[157]

If oral iron is used, it should be in the form of one of the ionic iron salts, such as iron sulfate, fumarate, or gluconate, because they are the cheapest and provide known amounts of elemental iron. Iron polysaccharide, which is more expensive, is no better tolerated (no less nausea, vomiting, or abdominal discomfort leading to discontinuation) than ionic iron salts.[204] Despite the perception by some that iron polysaccharide is more effective than the other iron salts, there have been no well-designed clinical studies which support that perception. In one study in which iron polysaccharide was one of four oral iron preparations given to Epoetin-treated hemodialysis patients,[150] this form of iron was associated with the smallest rise in mean Hct and the only mean Hct that was not significantly increased from baseline after 6 months of therapy.

When food is eaten within 2 hours before or 1 hour after an oral iron supplement, the food will reduce iron absorption by as much as one half.[205] Aluminum-based phosphate binders can also reduce iron absorption.[206] Ascorbic acid does not improve ferrous iron absorption.[207]

Patients who have difficulty tolerating oral iron supplements may benefit from smaller, more frequent doses, starting with a lower dose and increasing slowly to the target dose, trying a different form or product, or taking the supplement at bedtime.

Table IV-6 provides information on the amount of elemental iron in different preparations and the monthly cost of taking 200 mg of elemental iron per day.

The standard oral iron supplement in a child is 2 to 3 mg/kg/day of elemental iron in divided doses. There are oral liquid iron preparations that might be more applicable for young pediatric patients than the solid dose forms noted in Table IV-6.

IV. Administration of Epoetin

BACKGROUND

When Epoetin was administered during the initial clinical trials in the United States to patients with CKD, it was not known whether it would be effective and at what dose. Therefore, to assure that 100% of the dose would be available to stimulate erythropoiesis, Epoetin was administered intravenously. Subsequently, pharmacokinetic studies noted that subcutaneous (SC) administration provided elevated blood levels of Epoetin longer than the same dose given intravenously. In most countries outside of the United States, Epoetin is administered subcutaneously to most CKD patients. When the data from the many studies comparing IV to SC Epoetin are analyzed, the SC route of administration is as effective or more effective in the majority of patients than if Epoetin is given IV. Therefore, the Anemia Work Group recommends that SC Epoetin be the preferred route of administration.

GUIDELINE 11

Route of Administration of Epoetin

A. Epoetin should be administered subcutaneously (SC) in CKD and peritoneal dialysis patients. (**Opinion**)

B. The most effective route of Epoetin administration is SC in hemodialysis patients. (**Opinion**)

C. When Epoetin is given SC, the site of injection should be rotated with each administration. (**Opinion**)

GUIDELINE 12

Initial Epoetin Administration

A. SC Administration (**Evidence**)

1. When Epoetin is given SC to adult patients, the dose should be 80 to 120 units/kg/wk (typically 6,000 units/wk) in two to three doses per week.

2. Pediatric patients <5 years old frequently require higher doses (300 units/kg/wk) than older pediatric patients and adults.

B. IV Administration (**Evidence**)

If the initial administration of Epoetin is IV for hemodialysis patients, the dose should be 120 to 180 units/kg/wk (typically 9,000 units/wk), given in three divided doses.

RATIONALE FOR GUIDELINES 11 AND 12

Route of Administration of Epoetin

For normal subjects as well as CKD patients, SC administration of Epoetin has more favorable pharmacodynamics than IV administration,[209-213] despite the incomplete absorption of Epoetin following SC administration (bioavailability approximately 20%). On the other hand, because of the greater discomfort patients experience from SC compared to IV injections, it is likely that Epoetin would always be administered intravenously to hemodialysis patients, were it not for the relatively high cost of Epoetin.

In CKD and peritoneal dialysis patients, it is inconvenient as well as costly to administer Epoetin intravenously. In addition, veins need to be protected from venipuncture so that they are available for future hemodialysis access sites. Therefore, SC administration of Epoetin is preferable in these patients.

Numerous studies have examined the variation in effectiveness of Epoetin related to whether it is administered SC or IV. Thirty-six published studies on this topic involving 2,028 patients showed that, on average, the dose of Epoetin required to maintain a given Hct at 33% was lower (range, 0% to 68%) when Epoetin was administered subcutaneously compared to intravenously.[103,145,170,212-245] Two recent studies confirm the variability of response whether Epoetin is given SC or IV. In the largest study to date, a parallel group study in US male veterans, on average, the dose of Epoetin needed to maintain the Hct between 30% and 33% was more than 30% lower with SC than IV administration.[246] However, 23% of the 208 patients required more Epoetin when switched from IV to SC administration. A European study noted that when the route of administration in 15 patients was shifted from SC to IV (which differs from the protocol of most comparative studies), there was no difference in the mean thrice weekly dose of Epoetin or mean Hct during 6 months of therapy at each route of administration.[247]

Although most of the available studies had relatively small sample sizes and often had other methodological limitations, the aggregate data suggest several conclusions.

1. In a group of patients, such as all patients

receiving hemodialysis in a dialysis center, administration of Epoetin via the SC route appears to be more efficient than IV administration, ie, target Hgb and/or Hct levels are able to be maintained with a lower weekly Epoetin dose (15% to 50% lower) when the SC route is used.

2. The frequent administration of Epoetin appears to be more efficient, ie, administration of Epoetin on a two to three times per week basis appears to allow lower total weekly doses than administration once per week. However, the administration of Epoetin on a daily basis is no more effective than administration three times per week.[33,106] Thus, from a physiologic standpoint, Epoetin therapy should be initiated subcutaneously two to three times per week. Although two to three times per week SC administration is more efficient than once weekly administration, once weekly administration is more convenient for many CKD patients. In addition, Medicare currently does not reimburse for Epoetin use in CKD patients who are not dialysis dependent unless it is given in the physician's office. (Home administration currently is not reimbursed for Medicare patients.) The Anemia Work Group strongly encourages a change in this policy. Once the target Hgb/Hct has been achieved, it may be possible, for purposes of convenience, to administer Epoetin SC once weekly, or less often, in CKD, peritoneal dialysis, and hemodialysis patients.

There are insufficient data in the literature to make a recommendation for a specific site of administration of Epoetin. Therefore, it would seem prudent to rotate the site of injection with each administration.

Dose of Epoetin

When selecting the initial dose of Epoetin, the goal is to achieve the target Hgb/Hct within a 2- to 4-month period (corresponding to the lifespan of red blood cells in CKD) through the induction of a slow, steady increase of the Hgb/Hct. Ideally, that dose will turn out to be the dose necessary to maintain the Hgb/Hct at the target value.[248]

Since it is not possible to accurately predict the fraction of patients who will respond adequately to any dose of Epoetin, it will be necessary to monitor each patient's response to optimize the dose of Epoetin (see recommendation in Guideline 15: Monitoring of Hemoglobin/Hematocrit During Epoetin Therapy).

In pediatric PD patients, the median weekly Epoetin dose required to maintain a target Hct of 28% to 30% was 136 units/kg/wk in those older than 15 years.

A higher dose requirement for pediatric patients <5 years has been noted in two multicenter trials.[170,249] The basis for this difference has not been established. On the other hand, 19 of 22 children (peritoneal dialysis [10], hemodialysis [2], and chronic kidney function impairment [10]) between the ages of 4 months to 16 years (mean, 9 years) achieved target Hgb (9 to 11 g/dL) after 4 months of 50 U/kg of Epoetin given SC, twice weekly.[23]

GUIDELINE 13

Switching From Intravenous to Subcutaneous Epoetin

A. For hemodialysis patients who are being switched from IV to SC administration of Epoetin but have not yet achieved the target Hgb/Hct, the total weekly IV dose should be administered SC in two to three divided doses. (**Evidence**)

B. For hemodialysis patients who are being switched from IV to SC administration of Epoetin after achieving the target Hgb/Hct, the initial weekly SC dose should be two-thirds the weekly IV dose. (**Opinion**) Subsequent dose adjustments should be made as recommended in Guideline 16: Titration of Epoetin Dosage.

Rationale In the majority of hemodialysis patients, the erythropoietic response to a particular Epoetin dose will be greater with SC than with IV administration.[212,215,221,225,232,239] Simple conversion of the IV dose to a SC dose in patients who are not yet at the desired target Hgb/Hct will, therefore, in most patients, produce a subsequent increase in the Hgb/Hct.

Table IV-7. Advantages of Subcutaneous Versus Intravenous Epoetin Administration

Advantages of Subcutaneous Epoetin Administration
1. Most patients require less Epoetin via SC compared to IV route.
2. When given SC, Epoetin may be administered in many patients one to two times per week, thus reducing administration cost to facility.
Advantages of IV Epoetin Administration
1. No patient discomfort.
2. Most clinical experience (in the United States).

Studies have indicated that Epoetin requirements are, on average, about 15% to 50% less with SC dosing than with IV dosing.[212,215,221,225,232,239] Therefore, to avoid an unwanted increase in Hgb/Hct, approximately a 33% reduction in weekly dose should be made when converting from IV to SC administration if a stable target Hgb/Hct has already been achieved (see Guideline 11: Route of Administration of Epoetin). There is tremendous clinical variability, however, and some patients may require more Epoetin when administered SC compared to IV.[232] Careful monitoring of the response to Epoetin therapy and individual titration of the dose will be necessary after conversion of hemodialysis patients from IV to SC administration of Epoetin to achieve and maintain the target Hgb/Hct. If, after conversion, the weekly SC dose is greater than the previous weekly IV dose, the IV route of Epoetin administration should be resumed.

GUIDELINE 14

Strategies for Initiating and Converting to Subcutaneous Epoetin Administration

The use of the strategies listed below is suggested to increase patient acceptance of SC administration of Epoetin: (**Opinion**)

- When patients begin dialysis treatments, continue Epoetin administration subcutaneously.
- Educate hemodialysis patients on the advantages of SC administration (improved Hgb/Hct response and economic savings).
- Establish a unit-wide policy under which all hemodialysis patients are started on SC administration at the same time.
- Use the smallest possible gauge needle for injection (eg, 29 gauge).
- Use a multidose Epoetin preparation that contains benzyl alcohol.
- Divide the doses (a smaller volume for injection may reduce discomfort).
- Administer a single, weekly injection to patients receiving a small dose.
- Rotate injection sites between upper arm, thigh and abdominal wall areas.
- Encourage patients to self-administer Epoetin when possible.

Rationale It is impractical to administer Epoetin to CKD or PD patients intravenously, for reasons of staff and patient convenience. It is reasonable to continue SC administration after hemodialysis is initiated.

Successful implementation of SC Epoetin in hemodialysis units can be facilitated by several actions. Patients should be educated regarding the improved Hgb/Hct response, that is, achieving the target Hgb/Hct with less Epoetin.

Once all patients in a dialysis unit have been educated about the rationale for SC Epoetin administration (summarized in Table IV-7), it may be helpful to switch all patients from IV to SC at the same time. Otherwise, patients who have been used to receiving IV Epoetin who are reluctant to change to SC Epoetin might undermine efforts to put new hemodialysis patients on SC Epoetin.

Considering the drawbacks of frequent needle sticks, efforts should be undertaken to minimize discomfort associated with SC administration. Stinging may be associated with SC injection of Epoetin alfa, and has been attributed to the presence of a citrate buffer in the single-use vial. The multidose vial of Epoetin alfa contains the preservative benzyl alcohol, which acts as a local anesthetic and reduces the stinging. This preparation has been better tolerated than the single-use vial when Epoetin alfa is given SC.[250]

Additional strategies to minimize discomfort include use of the smallest gauge needle possible; a small injection volume, which can be accomplished by using the 10,000 units/mL multidose vial and administering Epoetin in three divided doses per week, or, for those patients requiring small doses (eg, $<$3,000 units/wk), reducing the frequency of administration to once weekly. Patients could be encouraged to participate in their own care by doing self-injections of Epoetin. Patients can control some of the discomfort that may accompany SC injections by controlling the speed of delivery of the injection. HCFA reimbursement policy will need to be altered so that self-injections outside of the dialysis unit are covered by Medicare.

GUIDELINE 15

Monitoring of Hemoglobin/Hematocrit During Epoetin Therapy

For purposes of monitoring response to Epoetin, Hgb/Hct should be measured every 1 to 2 weeks following initiation of treatment or follow-

ing a dose increase or decrease, until a stable target Hgb/Hct and Epoetin dose have been achieved. Once a stable target Hgb/Hct and Epoetin dose have been achieved, Hgb/Hct should be monitored every 2 to 4 weeks. (**Opinion**)

Rationale There are no reported studies that have systematically compared different protocols (ie, different frequencies of Hgb/Hct measurements) for monitoring the Hgb/Hct response to Epoetin therapy. Therefore, a single most clinically and/or cost-effective protocol cannot be based on data reported in the medical literature. With the doses of Epoetin recommended in these guidelines, and with optimal iron stores, the absolute rise in Hgb can be expected to be about 0.3 g/dL (0.2 to 0.5 g/dL) per week (hematocrit rise of 1% per week [typical response range, 0.5% to 1.5% per week]).[65,73,103,251-254] The dose-response range is wide, however. Weekly testing of Hgb/Hct is recommended following initiation of Epoetin, or an Epoetin dose adjustment, to detect changes in Hgb/Hct. Less frequent testing (ie, only every 2 weeks or monthly) could miss the very rapid erythropoietic response or the poor response and prevent an earlier dose adjustment. More frequent testing is not necessary (see Guideline 16: Titration of Epoetin Dosage).

GUIDELINE 16

Titration of Epoetin Dosage

If the increase in Hct after initiation of Epoetin therapy or after a dose increase has been <2 percentage points over a 2- to 4-week period, the dose of Epoetin should be increased by 50%. If the absolute rate of increase of Hgb/Hct after initiation of Epoetin therapy or after a dose increase exceeds 3 g/dL (or 8 Hct percentage points) per month (eg, an increase from a Hgb 7 to 10 g/dL or Hct change from 20% to 28%), or if the Hgb/Hct exceeds the target Hgb/Hct, reduce the weekly dose of Epoetin by 25%. When the weekly Epoetin dose is being increased or decreased, a change may be made in the amount administered in a given dose and/or the frequency of dosing (if given SC). (**Opinion**)

Rationale Several regimens have been described for adjusting the Epoetin dose until a target Hgb/Hct and stable maintenance Epoetin dose have been achieved. There are no reported studies, however, which have systematically compared different Epoetin dose adjustment protocols. Therefore, a single most effective and/or cost-effective protocol cannot be based on data reported in the medical literature. The dose adjustment strategies the Anemia Work Group recommends are similar to those which have been used safely and effectively in clinical trials.[65,73,251,253] The Epoetin dose increases recommended will also avoid unnecessary delays in obtaining a desired erythropoietic response.

A recommendation as to whether Epoetin should be withheld (ie, not given for some period of time) before reducing the Epoetin dose cannot be based on data from the medical literature. A distinction, though, should be made between the "rapid responder" (ie, a patient whose Hct has increased >8 percentage points in a month) and the patient who approaches the target Hgb/Hct gradually. In the former case, Epoetin should be withheld if the target has been reached and resumed 1 to 2 weeks later at 75% of the original dose, or maintained at the same dose but at a reduced frequency, if given SC. When the rate of rise in Hgb/Hct has been slower and the target range is about to be exceeded, withholding Epoetin can result in a "roller-coaster" effect. Therefore, in the latter instance, the dose should either be reduced or the frequency of SC administration should be reduced rather than omitting Epoetin therapy in order to stabilize and maintain the Hgb/Hct in the target range.

GUIDELINE 17

Inability to Tolerate Subcutaneous Epoetin; IV Epoetin Dose

When a hemodialysis patient is unable to tolerate SC administration of Epoetin, IV administration should be used. The IV Epoetin dose should be 50% higher than the SC dose, if known, or 120 to 180 units/kg/wk (typically 9,000 units/week), given in three divided doses. (**Opinion**)

Rationale Despite the best efforts of physicians and dialysis staff to educate patients regarding the value of SC Epoetin administration and to minimize discomfort associated with SC administration, there may be some patients who will not accept SC administration. This may be true, for example, in the case of the occasional patient

who requires very large doses of Epoetin, since SC administration of a large volume can be painful, or in the patient who develops recurrent ecchymoses and hematomas. When IV Epoetin is required, the weekly dose should be given in divided doses during each dialysis treatment. Once weekly IV administration of Epoetin results in a lower Hgb/Hct response, and a 25% increase in Epoetin requirements, compared with three times per week administration.[255] If Epoetin is given IV, it is best to inject it into either the arterial or venous blood lines (ie, the "ports") at any time during the hemodialysis procedure. Injection of Epoetin into the venous drip chamber of the Fresenius delivery system should be avoided since this can result in "trapping" and incomplete mixing with the patient's blood.[256]

On average, studies have shown comparable Hgb/Hct response with a SC dose which is two thirds of the IV dose. Therefore, the IV Epoetin dose should be 50% higher than the SC dose.[103]

GUIDELINE 18

Intraperitoneal Epoetin Administration

For peritoneal dialysis patients in whom SC or IV administration of Epoetin is not feasible, intraperitoneal (IP) administration may be considered. IP administration must be done into a dry abdomen or one with a minimal amount of dialysate.

IP dose requirements may be higher than those associated with IV or SC administration. (**Evidence**)

Rationale Epoetin administered into the abdominal cavity will be diluted if mixed with dialysate, thus slowing its absorption.[257] Perhaps for this reason, Epoetin doses are higher with IP administration, if mixed with dialysate, than with either IV or SC administration[210]; a "dry" abdomen results in better absorption.[257] For example, in pediatric patients, if Epoetin is administered intraperitoneally into a full dialysate dwell volume, absorption of Epoetin is less than 50% of that attained with SC administration, but absorption is enhanced if instilled with a small amount (50 mL) of dialysate.[258] Therefore, in pediatric patients, if IP administration of Epoetin is used, it is best to infuse it into a "dry" abdomen or one with a minimal amount of dialysate.

GUIDELINE 19

Epoetin Dosage Perioperatively or During Intercurrent Illness

A decision to continue or increase the Epoetin dose must be made on an individual basis in patients receiving Epoetin who undergo surgery, develop significant acute intercurrent illness, or require transfusion of red blood cells for acute blood loss. (**Opinion**)

Rationale Anecdotal observations suggest that the erythropoietic response to Epoetin may be reduced in patients who have significant intercurrent illness (infection, malignancy, inflammatory diseases) or who undergo surgery.[29,259-262] There are no studies available which support a specific recommendation as to whether the Epoetin dose should be discontinued, maintained, or increased to try to obtain a particular erythropoietic response in such patients, particularly upon hospitalization, or in patients in whom red blood cell transfusions are required for acute blood loss. Continuation of Epoetin at a dose at least equal to that which the patient was receiving prior to development of an acute illness or surgery may allow for more prompt resumption of erythropoiesis once the intercurrent illness has resolved.

Following successful renal transplantation, erythropoietin production by the transplanted kidney is often delayed for up to 8 to 30 days,[263-265] so full correction of anemia may not occur for 2 to 3 months after surgery. There are no data indicating that Epoetin administration during the immediate posttransplant period is of benefit.

V. Inadequate Epoetin Response

BACKGROUND

Ninety-six percent of patients will respond to Epoetin at 450 units/kg/wk IV (a dose expected to produce a comparable response to 300 units/kg/wk administered SC[103]) within 4 to 6 months, provided that there are adequate iron stores.[65] Therefore, an inadequate response to Epoetin therapy is defined as failure to achieve target Hgb/Hct in the presence of adequate iron stores at a dose of 450 units/kg/wk IV or 300 units/kg/wk SC within 4 to 6 months, or failure to maintain target Hgb/Hct subsequently at that dose. However, since there is a wide variability in dose response to Epoetin, an individual patient may respond to as little as 75 units/kg IV (or 50 units/kg SC) per week.

GUIDELINE 20

Causes for Inadequate Response to Epoetin

The most common cause of an incomplete response to Epoetin is iron deficiency.

In the iron-replete patient with an inadequate response to Epoetin, the following conditions should be evaluated and treated, if reversible: (**Evidence**)

1. Infection/inflammation (eg, access infections, surgical inflammation, AIDS, SLE)
2. Chronic blood loss
3. Osteitis fibrosa
4. Aluminum toxicity
5. Hemoglobinopathies (eg, alpha and beta thalassemias, sickle cell anemia)
6. Folate or vitamin B12 deficiency
7. Multiple myeloma
8. Malnutrition
9. Hemolysis

Rationale Iron deficiency has been reviewed in Guidelines 5, 6, 7, and 8. A brief review of the other potential causes of Epoetin resistance outlined above follows. The general approach to treatment of patients refractory to Epoetin should include identification and reversal of potentially treatable causes of resistance. When the cause of Epoetin resistance is untreatable, either progressively increase the Epoetin dose in an attempt to reach or maintain the target Hgb/Hct, transfuse with red blood cells (see Guideline 23: Red Blood Cell Transfusions in Dialysis Patients with Chronic Renal Failure) or accept an Hgb/Hct below the target level.

The nine conditions listed in this guideline have been documented to be potential reasons for inadequate response to Epoetin therapy in the adequately dialyzed, iron-replete patient. Of these, the first four are the most commonly encountered in the dialysis patient. The other five are less common and should be considered only if the first four have been excluded.

1. Infection and inflammation can markedly impair responsiveness to Epoetin; responsiveness is usually restored upon resolution of the underlying problem.[29,259,266-270] The differential diagnosis is extremely broad, encompassing all infectious disorders, including access infections, AIDS, rheumatologic disorders, and surgical inflammation (including vascular access surgery). In pediatric patients on CAPD, peritonitis may exert a protracted suppressive effect on the response to Epoetin.[270] The pathophysiology of inflammatory reticuloendothelial blockage is gradually being elucidated and may relate to the inhibition of erythropoiesis, mediated by inflammatory cytokines, such as tumor necrosis factor and interleukin-1.[267,268] An elevated C-reactive protein level, often associated with inflammation and/or infection, has been a predictor of resistance to Epoetin.[271,272]

2. Chronic blood loss, regardless of cause, results in iron deficiency and thus impaired Epoetin response.[35] Blood loss should always be suspected in patients who require increasing doses of Epoetin to maintain a stable Hgb/Hct, in patients whose Hgb/Hct levels are falling, and in patients with failure to augment iron stores in the face of repetitive intravenous iron loading. The appropriate approach to the evaluation of this problem is addressed in Guideline 6: Target Iron Level, and Guideline 7: Monitoring Iron Status, and Guideline 8: Administration of Supplemental Iron.

3. Osteitis fibrosa impairs response to Epoetin by replacing active marrow erythroid elements with fibrosis. Although the best study does not demonstrate a statistically significant relationship between serum levels of intact parathor-

mone (iPTH) and Epoetin dose, there is a direct relationship between the degree of fibrosis and the amount of Epoetin needed to maintain a stable Hct.[273]

4. Aluminum intoxication affecting the marrow can either prolong the treatment time required to reach the target Hgb/Hct or necessitate higher Epoetin doses, but has not been shown to cause absolute resistance to therapy.[277-279]

5. *Hemoglobinopathies:* Patients with sickle cell disease respond poorly to Epoetin therapy, even when high doses of Epoetin are used over long treatment periods. In hemoglobin SS and SC diseases, Epoetin results in release of reticulocytes containing predominantly hemoglobin S, with little if any increment in the more stable hemoglobin F.[280-282] Both alpha and beta thalassemia may respond poorly to Epoetin. Alpha thalassemia is more common among Asians and those of Asian ancestry. Treatment of alpha thalassemia with Epoetin may increase Hgb slowly, with effective therapy usually requiring very high doses over a long period.[283,284]

6. *Folate and vitamin B12 deficiency:* Folic acid and vitamin B12 are essential for optimal Hgb synthesis. While most of the available literature suggests that effective Epoetin therapy does not require concomitant vitamin B12 and folate supplementation, the latter is water soluble and dialysate losses may exceed intake in poorly nourished patients. Therefore, loss of responsiveness to Epoetin requires investigation of cofactor adequacy.[285-288] One study, however, suggests that concomitant folate administration improves Epoetin response.[286] Specifically, this study suggests that even if folate levels are adequate at the inception of Epoetin therapy, macrocytosis and poor response will develop without continuous cofactor replacement.[289] The presence of macrocytosis must be interpreted with caution, however, since Epoetin therapy is often associated with macrocytosis, due to shifting of immature (large) reticulocytes into circulation. Iron overload is also associated with macrocytosis.[154]

7. *Multiple myeloma:* Reports on the effectiveness of Epoetin treatment in this setting are few, contain small numbers of patients, and have variable results. Poor response (increases in Hgb from 5.9 to 6.2 g/dL) has been reported at doses of 125 units/kg/wk SC to 320 units/kg/wk SC in some patients,[290] although others appear not to require transfusions on regimens of 120 to 140 units/kg/wk.[291,292] The reason(s) for the varying effectiveness of these dosing schedules is unclear. Several reports have expressed concern over the potential for stimulation of malignant clone proliferation with chronic cytokine therapy (Endnote n).[290,293] Despite this potential concern, Epoetin is not contraindicated in the treatment of the anemia of patients with myeloma kidney disease.

8. *Malnutrition:* Low serum albumin is associated with low Hgb among dialysis patients. About one third of CKD patients have low albumin. While malnutrition is common in this population, any acute or chronic inflammatory condition may result in a low serum albumin.[294] The effect of nutritional status on Epoetin responsiveness in ESRD patients has received little attention.[295] Theoretically, protein and/or calorie malnutrition may result in the unavailability of needed substrate for protein synthesis in hematopoietic cells.

9. *Hemolysis:* Dramatic resistance to Epoetin therapy has been documented in anti-Nform hemolysis in the setting of chronic formaldehyde exposure[296] and with hemolysis resulting from multiple cardiac valve replacements.[296]

Other Potential Causes *Angiotensin-converting enzyme inhibitors (ACE-I):* There was initial concern that ACE-I would worsen the anemia of CKD because of its ability to diminish posttransplant erythrocytosis.[297] Subsequent reports provide conflicting information: three suggest that there is no inhibition of Epoetin by ACE-I,[298-300] whereas four brief reports and one recent study,[305] in which no other cause of Epoetin-resistance could be determined, concluded that ACE-I did inhibit the action of Epoetin.[301-304] The mechanism of action of such an effect, if present, is not known, but considerations include interference with native erythropoietin secretion,[304] blunting of the effect of Epoetin, or direct inhibition of the erythroid marrow response to Epoetin. Patients receiving ACE-I who are treated with Epoetin should be monitored for possible resistance to therapy and the Epoetin dosage should be adjusted in order to sustain a stable Hgb/Hct. Malignancy may result in anemia. If

malignancies other than myeloma (addressed above) develop, and are thought to decrease the efficacy of Epoetin therapy, larger amounts of Epoetin are appropriate, since in general, the anemia of cancer patients (with normal renal function), requires larger doses of Epoetin than the anemia of CKD to obtain an erythropoietic response.[124]

GUIDELINE 21

When to Obtain a Hematology Consultation

If Epoetin resistance occurs in the absence of the conditions listed in Guideline 20: Causes for Inadequate Response to Epoetin, a hematology consultation is recommended. (**Opinion**)

Rationale If all of the conditions listed in Guideline 20: Causes for Inadequate Response to Epoetin, have been excluded, determination of the cause of Epoetin resistance will likely require the expertise of a specialist in hematology.

GUIDELINE 22

Epoetin-Resistant Patients

Anemia in Epoetin-resistant patients should be treated in a manner similar to that in which dialysis patients were treated before recombinant human erythropoietin was available. (**Opinion**)

Rationale No therapy has been shown to be as effective as Epoetin in the treatment of the anemia of CKD. Other therapies have been shown to be either partially effective or ineffective, and many are associated with unacceptable side effects. While the following therapies have increased erythropoiesis in some dialysis patients not treated with Epoetin, there are insufficient data to support the conclusions that any of these therapies enhances the response to Epoetin when used as adjuvant agents in the Epoetin-resistant patient:

1. *Carnitine:* Reports suggesting that carnitine improves Epoetin response or permits reduction in its dose are anecdotal and involve only a few patients in each study.[306-308] One study comparing the dose-response to Epoetin in carnitine-treated and placebo-treated dialysis patients showed an enhanced response to Epoetin in 7 of 13 carnitine-treated patients,[309] whereas another study showed that only 8 of 19 patients might have had potentiation of Epoetin with carnitine administration, but iron supplementation might have been responsible for the improvement.[310] More controlled trials are needed with carnitine before definitive recommendations for its use as an adjuvant therapy can be made (see also K/DOQI guidelines on Nutrition).

2. *Androgens:* Studies designed to assess whether androgens enhance response to Epoetin are inconclusive (ineffective,[311] effective[312]). Another recent study indicates that the erythropoietic response to androgens in males over 50 years of age with ESRD is as effective as that to Epoetin (6,000 units/wk) in males under 50 years of age and in females, and is less expensive than Epoetin therapy over 6 months.[313] However, although androgen therapy may be less expensive than Epoetin, the risks and side-effects of primary androgen therapy alone,particularly in females, are unacceptable. The absence of convincing evidence of a clinical benefit associated with androgen therapy in combination with Epoetin argues against its use, particularly in light of the side effects.

3. *Dialysis prescription; dialysis efficiency; hemodialysis with biocompatible membranes:* This literature, too, is inconclusive. One report suggests that an inverse relationship exists between Epoetin dose and dialysis efficiency.[314] A recent study reported that a higher delivered dose of dialysis improves Epoetin effectiveness.[315] Its findings, however, are not convincing: the independent effects of higher Kt/V (small molecule clearance) on Epoetin response were not separated from those of biocompatible dialyzer membranes, the Epoetin treatment interval was short for the magnitude of response reported, and no control data were provided before the change in dialysis prescription was initiated. Another study reports that middle molecule clearance, not delivered dose measured by urea kinetic modeling, may enhance Epoetin responsiveness.[316] Hemodialysis for 445 patients in Tassin, France in which middle and small molecule clearances were greater than that in most dialysis centers (24 hours per week with Kiil dialyzers using cuprophane membranes with a mean Kt/V of

1.67) resulted in a mean Hct of 28.1% in the absence of Epoetin therapy.[317] While this is a higher mean Hct than that observed during the pre-Epoetin era in most dialysis centers that provided fewer weekly hours of hemodialysis, there are no data (as yet) showing that these patients now require less Epoetin to achieve higher Hct values than those treated at other dialysis centers. Whether the magnitude of the delivered dialysis dose, dialyzer membrane, or clearance of a specific surrogate solute has an effect on response to Epoetin in the patient who is not severely uremic remains unresolved and needs further investigation.

VI. Role of Red Blood Cell Transfusions

GUIDELINE 23

Red Blood Cell Transfusions in Patients With Chronic Renal Failure

Red blood cell transfusions are indicated in:

A. The severely anemic patient with recognized symptoms or signs due to the anemia, eg, the patient with acute blood loss associated with hemodynamic instability (**Opinion**)

B. The Epoetin-resistant patient who has chronic blood loss (**Opinion**)

Rationale The following principles regarding red blood cell transfusion, promulgated by the American College of Physicians,[318] should be followed when determining the need for transfusions:

1. Determine the reversibility/nature of anemia so that reversible causes may be treated.

2. Determine which, if any, symptoms or signs are likely to be reversed by giving red blood cell transfusions. If none can be identified, do not transfuse.

VII. Possible Adverse Effects Related to Epoetin Therapy

BACKGROUND

During the initial Epoetin clinical trials, most of which were uncontrolled, a number of adverse effects were reported. Some of these adverse effects have not been observed consistently in subsequent experience with Epoetin, suggesting that Epoetin is not the direct cause of these adverse effects. Moreover, these adverse effects have not been observed when Epoetin is used in the treatment of non-renal anemias. However, because there has been much discussion of these adverse effects in the past, these "possible" adverse effects are reviewed here.

GUIDELINE 24

Possible Adverse Effects Related to Epoetin Therapy: Hypertension

Blood pressure should be monitored in all patients with CKD, particularly during initiation of Epoetin therapy. Initiation of anti-hypertensive therapy or an increase in anti-hypertensive medication, and reduction in Epoetin dose if there has been a rapid rise in Hgb/Hct, may be required to control an increase in blood pressure related to Epoetin therapy. (**Evidence**)

Rationale In our review of 47 publications, 785 of a total of 3,428 patients (approximately 23%) developed hypertension or an increase in blood pressure during treatment with Epoetin.[22,34,38,59,102,106,235,245,252,292,319-355] While many factors thought to enhance a pressor response to Epoetin have been proposed,[356] no single factor has been consistently linked to this response in the minority of CKD patients in whom it occurs. Several recent studies, however, have studied the role of the endothelium and/or vascular smooth muscle cell in the hypertensive reaction, since EPO receptors are present on endothelial cells.[357] One in vitro study showed that Epoetin (250 U/ml) inhibited IL-1β–induced apoptosis of vascular smooth muscle cells which might induce hypertension since nitric oxide production is inhibited.[358] However, another study showed that relatively long-term exposure of human endothelial cells in culture with Epoetin (4 U/mL) for 1 to 6 days increased nitric oxide synthase mRNA levels, but not endothelin-1 levels, suggesting that Epoetin has a vasodilatory effect on the endothelium.[359] These in vitro studies are then contrasted with recent in vivo studies suggesting that a single dose of 100 U/kg of Epoetin results in an increase in mean arterial pressure (MAP) when Epoetin is administered IV, but not when it is administered SC.[360] The increase in MAP is associated with an increase in the ratio of plasma endothelin to proendothelin[360] and may be associated with elevated cytosolic ionic calcium and nitric oxide resistance.[361] The incidence of hypertension associated with Epoetin is not associated with either the dose of Epoetin or whether a normal Hct is achieved.[80,129] The hypertensive response is not observed in anemic patients without renal disease who are treated with Epoetin.[124] Therefore, the cause of the Epoetin associated clinical hypertension remains unresoved to date. New onset or worsening hypertension in association with Epoetin therapy is thought to be related to an increase in vascular wall reactivity, along with hemodynamic changes related to an increasing red blood cell mass. Initiation of anti-hypertensive therapy or an increase in the dose of anti-hypertensive medications, intensified ultrafiltration if there is evidence of extracellular volume expansion, and/or a reduction in Epoetin dose may be required to control an increase in blood pressure related to Epoetin therapy. It is not necessary to withhold or discontinue Epoetin therapy due to hypertension unless such hypertension is refractory to aggressive blood pressure management. There is no evidence that increased blood pressure associated with the use of Epoetin should be treated any differently than hypertension in dialysis patients who are not treated with Epoetin. However, if hypertensive encephalopathy occurs, with or without seizures, Epoetin should be discontinued until clinical stability is achieved.

GUIDELINE 25

Possible Adverse Effects Related to Epoetin Therapy: Seizures

There is no need to restrict patient activities due to a concern about new onset seizures or a change in seizure frequency in patients being treated with Epoetin. A prior history of seizures is not a contraindication for Epoetin use. (**Evidence**)

Rationale The initial and largest multicenter study with Epoetin in the United States[65] noted a higher incidence of seizures during the first 3 months of the study compared to historical controls. Ten subsequent studies which analyzed the incidence of seizures among patients receiving Epoetin found the mean percentage of patients with seizures to be 3% (59 of 2,203 patients), with a range of 0% to 13%.[22,322,329,342,348,352,362-365] None of these studies reported the presence or absence of seizure history prior to the use of Epoetin. There is only one controlled study which has examined the incidence of seizure activity in dialysis-dependent ESRD patients in the absence of Epoetin therapy. In this study, one out of 20 patients (5%) not on Epoetin had a seizure.[364] Except in the case of patients with hypertensive encephalopathy, there appears to be no evidence of an increased risk of seizures in CKD patients treated with Epoetin when appropriate dosage and titration recommendations are followed. Use of Epoetin in the patient with a prior history of seizures is not contraindicated since there is no evidence of an increase in the risk of seizure in ESRD patients receiving Epoetin therapy.

GUIDELINE 26

Possible Adverse Effects Related to Epoetin Therapy: Increased Clotting Tendency

A. There is no need for increased surveillance of access thrombosis in hemodialysis patients with either native fistulae or synthetic grafts when patients are treated with Epoetin. (**Evidence**)

B. Epoetin-treated hemodialysis patients do not need more heparin than patients not treated with Epoetin. (**Evidence**)

Rationale In our review of 26 studies in which 4,110 hemodialysis patients were enrolled, the average incidence of thrombosis of any access in patients on Epoetin was 7.5%.[22,34,38,39,65,74,228,245,299,322,347,348,352,362,366-376] The target Hcts in these studies were $<$36%, but the mean achieved Hcts were approximately 34%. In general, the fewer patients enrolled in a study, the higher was the reported incidence of access thrombosis. Most of these papers cited either historical controls, or used patients as their own controls, pre- and post-Epoetin use. No difference was reported in the rate of access thrombosis in one study that compared patients receiving and not receiving Epoetin.[370]

There is evidence that Epoetin therapy does not increase the risk of progressive stenosis in native fistulae.[377] The evidence that Epoetin therapy increases the risk of PTFE graft thrombosis is equivocal (Endnote o). In the recent Amgen study of hemodialysis patients with heart disease (CHF and/or ischemic heart disease), there was a significant increase in thromboses of both native fistulae and synthetic arteriovenous grafts in patients randomized to a target Hct of 42% $\pm$ 3%, compared to a target Hct of 30% $\pm$ 3%. However, there was no correlation between the Hct level achieved, the dose of Epoetin, and the occurrence of access thrombosis.[80]

There are many studies indicating that clotting function improves as the Hct increases to above 30% in dialysis patients.[378] However, there is no evidence from the large, North American multicenter studies[65,73] that increasing the red blood cell mass with Epoetin increases dialyzer heparin requirements, although a 20% to 40% increase in heparin requirements was noted in one European study.[374] A recent autopsy study found that, over a 10-year period in which the percentage of hemodialysis patients receiving Epoetin increased, there was no increase in the prevalence of preterminal pulmonary thromboembolism.[379]

One study of 85 diabetic patients on peritoneal dialysis reported that patients treated with Epoetin had an increased incidence of peripheral vascular disease and an increased risk of serious limb or digit ischemia.[380] This study was small, retrospective and had many potential confounders. In addition, no clotting studies were performed. A larger prospective randomized study would need to confirm these findings before a caution regarding use of Epoetin in diabetic PD patients could be recommended.

GUIDELINE 27

Possible Adverse Effects Related to Epoetin Therapy: Hyperkalemia

Epoetin-treated dialysis patients do not need more intensive potassium monitoring than patients not treated with Epoetin. (**Evidence**)

Rationale While serious hyperkalemia was observed in the early experience with Epoetin,[35] the more recent data indicate that the incidence

of hyperkalemia is not significantly higher in Epoetin-treated patients. Our review of five papers with a cumulative total of 1,167 patients revealed only 12 cases of hyperkalemia. In the two series[322,329] accounting for 1,000 patients, the incidence of hyperkalemia was less than 1%. When patients receiving Epoetin were compared to patients not receiving Epoetin,[370,376] the incidence of hyperkalemia in Epoetin-treated patients was less than or equal to the incidence in non–Epoetin-treated patients in two of the three studies.

VIII. Endnotes

SECTION I: ANEMIA EVALUATION

(a)

Thirty-three patients with severe chronic kidney disease (creatinine clearance of 10 to 14 mL/min) were moderately anemic with mean Hgb 10g/dL.[52] These patients were treated with oral iron initially, with minimal response, and then received 50 mg of IV ferric saccharate every week for a total of 1,000 mg. Twenty-two, or two thirds of the patients, were classified as responders in that their Hgb increased from 9.9 to 11.1 g/dL (Hct from 29.4% to 32.4%). The responding patients had baseline mean transferrin saturation values of 21.9% and baseline mean serum ferritin values of 94 ng/mL. The nonresponders had similar values. The authors recommended that enough IV iron should be given to increase the serum ferritin levels to 200 to 400 ng/mL and/or transferrin saturation values to between 25% and 35% before initiating Epoetin therapy.[52]

SECTION II: TARGET HEMOGLOBIN/HEMATOCRIT

(b)

In the Canadian study,[73] three groups of patients were studied: one placebo group and two Epoetin-treated groups with target Hgb values of 10.2 $\pm$ 1.0 g/dL and 11.7 $\pm$ 1.7 g/dL, respectively. The mean values for the physiologic tests of the higher target group at baseline (Hgb 7.1 $\pm$ 1.2 g/dL) were much higher than the mean values obtained in the other treatment group which reached the target Hgb of 10.2 $\pm$ 1.0 g/dL, thereby making the authors' conclusions difficult to interpret. In an Australian study,[74] cardiac index and heart rate were clinically and statistically significantly better in the group of patients reaching higher target Hgb. Quality of life was also better at the higher Hgb, but the difference failed to reach statistical significance,[75] possibly because of the relatively small number of patients.

(c)

Hgb levels among 107 patients without LVH were 11.9 $\pm$ 2.0 g/dL, whereas in 68 patients with LVH, Hgb levels were 11.0 $\pm$ 2.1 g/dL ($P = 0.0049$).[86] Sixty percent of the patients with an Hgb $\leq$11 g/dL had LVH.

(d)

It is now clear that the increased cerebral blood flow is a physiological response to a decrease in the total oxygen content of arterial blood.[381] In an in vivo study, cerebral blood flow and oxygen delivery were examined in eight normal volunteers whose Hct levels were decreased from a mean of 42.5% to 37.7% via phlebotomy and hemodilution.[382] Using PET scans and oxygen (O_2)[15] inhalation, a decrease in total oxygen content of arterial blood from 19.1 $\pm$ 1.0 to 16.9 $\pm$ 1.0 mL/dL ($P < 0.005$) was demonstrated. Despite an increase in cerebral blood flow, there was still a decrease in oxygen delivery to cerebral tissue. The authors concluded that optimal Hct for the human brain is that normally found at sea level. This finding was confirmed by another study in which 27 patients with ischemic cerebrovascular disease were studied with intracarotid isotope injection to determine cerebral blood flow and oxygen delivery between a Hct range of 31% to 53%. As shown previously, there was an inverse relationship between Hct and cerebral blood flow, but a linear relationship between Hct and oxygen delivery to brain tissue, with the maximal level of oxygen delivery occurring within a Hct range of 40% to 45%.

(e)

Of 1,410 hemodialysis patients observed before Epoetin was used therapeutically in Okinawa, Japan (April 1, 1988 to March 31, 1990), 25 had strokes and 3 had acute myocardial infarctions. Following the use of Epoetin (April 1, 1990 to March 31, 1993), 61 and 12 patients out of 1,916 hemodialysis patients had strokes or acute myocardial infarctions, respectively. These were highly statistically significant differences. Unfortunately, the Hct levels were not reported in the Epoetin-treated patients, although the target level was 30%. The conclusions of this study are considered flawed as noted in a letter to the editor of *Nephron*.[383] In response to this letter, the lead author on the study seems uncertain about his findings by stating "we do not think that EPO is the culprit of the observed increase in incidence of stroke/AMI," and yet also adds "we believe that the introduction of EPO and the changes in patient demographics caused the difference in the incidence of stroke/AMI."[384] These

authors had previously reported that the risk of cerebral hemorrhage in their hemodialysis patients was 10.7 times higher than the general Okinawa population,[385] an incidence not observed in the United States.

SECTION III: IRON SUPPORT

(f)

This conclusion is supported by data from the USRDS Dialysis Morbidity and Mortality Study (wave 1) for 1996, in which more than 50% of 2,613 dialysis patients in 1993 had TSAT levels of $<$20%, 36% had serum ferritin levels of $<$100 ng/mL, and 56% had serum ferritin levels of $<$200 ng/mL. Furthermore, only 11.2% of these patients had received IV iron, and 25% had received neither IV nor oral iron.[66]

(g)

Hemodialysis patients typically lose up to 15 to 25 mL of whole blood at each dialysis treatment (approximately 60 mL per week) as a result of retention of blood in the dialyzer and tubing, and phlebotomy for blood testing.[386,387] If such patients have a Hct of 36%, this constitutes an average loss of 3 mL of RBC per day. Average (in a normal subject) GI iron losses of 1 mg/day heighten depletion of iron stores, resulting in a total loss of at least 400 mg of iron over a 100-day period (an arbitrary duration used for calculation purposes only). Some patients, such as menstruating females, have even greater blood losses. Patients who undergo vascular access surgery or who have additional gastrointestinal bleeding often have cumulative iron losses exceeding 2 g/year. Yearly losses up to 6 to 8 grams have been documented.[133]

(h)

Since blood volume is approximately 8% of body weight, a 70 kg patient has a blood volume of approximately 5 to 6 L. At an Hct of 25%, this represents an RBC volume of 1,400 mL (5,600 mL $\times$ 25%). At an Hct of 35%, a blood volume of 5 to 6 L represents an RBC volume of 2,000 mL (5,600 mL $\times$ 35%). Thus, to increase the Hct of a 70 kg patient from 25% to 35%, a patient needs to produce 600 mL of red blood cells (2,000 mL minus 1,400 mL). Since each milliliter of newly synthesized RBCs contains 1 mg of iron, 600 mg of iron are needed to produce an increase in RBC volume of 600 mL. An alternative method for determining the iron requirement associated with Epoetin therapy has utilized a nomogram approach.[388]

(i)

Bone marrow biopsy specimens stained to assess iron are traditionally considered the "gold standard" measure of iron stores. It is not practical, however, to perform serial bone marrow biopsies to monitor the iron status of dialysis patients.

(j)

For example, a recent small study[137] found that 12% of hemodialysis patients who were functionally iron deficient had a TSAT $\leq$20%, and 4% of patients who were functionally iron deficient had a TSAT $\geq$30%. The same investigators concluded that 12% of patients who had a TSAT $<$15% were not iron deficient. However the protocol these investigators used for administering Epoetin and iron (the dose of Epoetin was decreased by 25% if the Hct was $>$34%, and the total amount of IV iron given was limited to one gram) could have resulted in an underestimate of patients who were functionally iron deficient. This same study[137] noted that 50% of patients who were functionally iron deficient had serum ferritin levels $<$100 ng/mL, while 10% of patients who were functionally iron deficient had serum ferritin levels $>$300 ng/mL. Although none of the patients who were functionally iron deficient in this small study had serum ferritin values $>$500 ng/mL, such patients have been reported.[35,142,145]

(k)

With the exception of two studies involving CAPD patients[134,161] and one study involving CKD subjects,[52] the studies summarized in Table IV-3 show the overall effects of regular IV iron administration in hemodialysis patients. Only mean values are depicted. The amount of IV iron is reported in milligrams per week. The frequency of iron administration varied from 3 times per week to once every other week. The duration of the studies is indicated by the number of months depicted. The first three studies showed the effects of IV iron in iron-deficient subjects. Eight studies by seven authors depicted the effects of IV iron on individuals considered to have adequate iron stores. In conjunction with the use of IV iron, the Hgb/Hct rose 19% $\pm$ 20% and the

dose of Epoetin decreased by 34% ± 27% in these 8 studies. Five of these studies had baseline TSAT values between 23% and 31%. The baseline serum ferritin levels of patients who responded to IV iron varied from 99 to 403 ng/mL. The serum ferritin values did not exceed 800 ng/mL.

(l)

Acquired iron overload developed in 15 adults with normal kidney function from 70 to 210 red blood cell transfusions and was associated with serum ferritin levels of 950 to 5,000 ng/mL.[389] Iron overload in dialysis patients (11 adults and 5 children) was associated with serum ferritin levels of 11,110 ± 1,679 ng/mL and 7,550 ± 3,088 ng/mL, respectively,[189] and in another series of 12 adult dialysis patients with iron overload, the serum ferritin and TSAT were 8,168 ± 1,265 ng/mL and 88.3% ± 4.9%, respectively.[190]

(m)

One report of 670 hemodialysis patients indicated that patients (n = 118) with serum ferritin levels 521 ± 775 ng/mL had more bacterial infections than did patients (n = 489) whose serum ferritin levels were 376 ± 529 ng/mL.[194] These patients were "iron-overloaded" presumably from previous transfusions, although no details were given concerning previous transfusions, parenteral iron use, or Hgb/Hct values. Only 15% of the patients were receiving Epoetin since this study was conducted over a 6-month period between September 1989 and February 1990, when Epoetin had just become available for clinical use in France. While the difference between the serum ferritin levels was significant ($P = 0.028$) between the two groups, the more important risk factors for infection were found to be a previous history of bacterial infection and the presence of a central venous dialysis catheter. It is difficult to exclude the role of transfusion-induced immunosuppression as the cause of the increased incidence of bacterial infections in the group with the higher serum ferritin levels. A later study by the same authors failed to confirm this relationship.[198]

SECTION V: INADEQUATE EPOETIN RESPONSE

(n)

Two hemodialysis patients with multiple myeloma relapsed in the setting of aggressive Epoetin therapy[290]; 1 patient relapsed, after a 6-month remission, with a new lytic lesion less than 1 month after initiating treatment at 100 units/kg. Urinary light chain excretion increased 10-fold (1.56 to 10.75 g/L) in a nondialysis patient following treatment with 4,000 units twice weekly; excretion reverted to pretreatment levels with discontinuation of Epoetin.[293] Two observations provide physiologic rationales for these clinical observations: erythropoietin receptors are expressed on human myeloma cells,[390] and nonerythroid marrow elements at the progenitor cell level respond to therapeutic doses of Epoetin in dialysis patients.[391,392]

SECTION VII: POSSIBLE ADVERSE EFFECTS RELATED TO EPOETIN THERAPY

(o)

The Canadian multicenter trial[393] suggests that Epoetin increases the risk of thrombosis in PTFE grafts. This study matched patients on Epoetin with similar patients not on Epoetin. It reports an incidence of graft thrombosis 2.2 times higher in Epoetin-treated patients with grafts versus patients with grafts who were not treated with Epoetin. The Epoetin-treated patients had lower serum albumin levels and a higher prevalence of cardiovascular disease. The authors controlled for length of time the grafts were used prior to initiation of Epoetin therapy, but did not mention the actual age of the grafts. There were 38 pairs of patients; the authors did not state the fate of the nine patients who had grafts and received Epoetin, but for whom they could not find a paired control. In addition, there was no correlation between risk of thrombosis and the baseline Hgb, the rise of Hgb, or the dose of Epoetin. The authors suggested that their findings should be "interpreted cautiously."

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X. Biographical Sketches of the NKF-K/DOQI Anemia Work Group Members

The following are brief sketches that describe the professional training and experience as well as principal business affiliations of the Work Group members. All Work Group members completed a disclosure statement certifying that any potential conflict of interest would not influence their judgement or actions concerning the NKF-K/DOQI.

Joseph Eschbach, MD (Work Group Chair), is Clinical Professor of Medicine at the University of Washington in Seattle, Washington and a private practice nephrologist at Minor & James Medical in Seattle. Dr. Eschbach, who has been treating patients with chronic kidney disease and doing research for 37 years, served as Director of the first home dialysis training center in the United States. He has lectured extensively on the pathophysiology and treatment of the anemia of chronic kidney disease and has written more than 100 articles on the subject. Dr. Eschbach has received multiple awards for his efforts to improve the quality of life for dialysis patients, including the David M. Hume Memorial Award, National Kidney Foundation (1995), and the Haviland Award of Excellence, Northwest Kidney Foundation (1991). He is a member of the Institute of Medicine of the National Academy of Sciences (1990).

Peter DeOreo, MD, FACP (Work Group Vice-Chair), is Medical Director and Chief Medical Officer of the Centers for Dialysis Care, Cleveland, Ohio. He and 40 other nephrologists in the Cleveland area are working to improve clinical outcomes for 1,000 patients. Dr. DeOreo is an Associate Clinical Professor of Medicine at Case Western Reserve University and is a member of the Division of Nephrology of University Hospitals of Cleveland. He has served on the Medical Review Board of network 22, and was Chairman of the Ad Hoc Committee on Dialysis Adequacy for Network 9. Dr. DeOreo is a member of the External Monitoring Committee for National Cooperative Peritoneal Dialysis Adequacy Study, serves on the Health Status Outcomes in ESRD Working Group, and was a participant in the Institute of Medicine's panel on measuring and managing quality in ESRD. He has published papers on quality improvement, care path development, dialysis adequacy, and patient-assessed functional health status measurement. Dr. DeOreo is an internist and consulting nephrologist for University MedNet.

John Adamson, MD, is currently the Executive Vice President for research and Director of the Blood Research Institute of the Blood Center of Southeastern Wisconsin in Milwaukee. He is also Professor (Hematology/Oncology) in the Department of Medicine at the Medical College of Wisconsin. Dr. Adamson received his M.D. degree from the University of California, Los Angeles. He then trained at the University of Washington, Seattle, and at the National Institutes of Health, Bethesda, Maryland, in the fields of internal medicine and hematology. Dr. Adamson is a Past President of the American Society of Hematology and the International Society for Experimental Hematology. In 1988, Dr. Adamson was designated a Clinical Research Professor of the American Cancer Society and elected Fellow, American Association for the Advancement of Science. He is the past Editor-in-Chief of *Blood*, past Editor of the *Journal of Cellular Physiology* and founding Editor of *Current Opinion in Hematology.* Altogether, he has authored or co-authored more than 400 scientific publications.

Jeffrey Berns, MD, FACP, is Associate Professor of Medicine at the University of Pennsylvania School of Medicine and Associate Chief of the Renal-Electrolyte & Hypertension Division at Presbyterian Medical Center of the University of Pennsylvania Health System in Philadelphia. Dr. Berns is a graduate of Case Western Reserve University School of Medicine and completed his Nephrology fellowship at Yale University. He has recently co-edited a book on renal aspects of HIV infection and is a co-editor of *Drug Prescribing in Renal Failure*, published by the American College of Physicians. Dr. Berns has published papers on a number of clinical topics including erythropoietin and iron treatment of anemia in dialysis patients, most recently on the effects of normal hematocrit levels on ambulatory blood pressures in hemodialysis patients, radiographic contrast-induced renal failure, and membranous nephropathy. He is involved in clinical research

studies with erythropoietin, novel erythropoietic stimulating protein and iron gluconate in dialysis patients. He reported receiving research grant funding from Amgen, Inc. and R&D Laboratories, Inc. and has received lectureship honoraria from Schein Pharmaceuticals.

Geraldine Biddle, RN, CNN, is the President of Nephrology Nurse Consultants. She is a certified Nephrology Nurse who has worked in the field of renal dialysis for more than 30 years and has held clinical, administrative, and faculty positions at major academic centers in the Northeast. In 1988, she began to work as a consultant to the Network of New York and, in 1994, to the Center for Clinical Measurement and Improvement, HSQB, HCFA. She served as Chairperson for the ESRD Forum of Networks CQI Workgroup, and on behalf of the workgroup wrote the *Guide for Improving the Quality of Care of Dialysis Patients*, a central component of the National Anemia Cooperative project. She worked with the FDA on the production of the first in a series of videotapes produced by the agency to address user errors in dialysis. The video, *Human Factors in Dialysis,* later won the Commissioner's Citation. Mrs. Biddle is a Certified Professional in Healthcare Quality and teaches quality management and CQI to dialysis staff at local, regional and national workshops. She is a former President of the American Nephrology Nurses' Association, Immediate Past-President of the NKF of Northeast New York, and presently serves as President of the World Foundation for Renal Care. Mrs. Biddle is a consultant to the ESRD Network of New York, and the HCFA Office of Clinical Quality Management.

Thomas Comstock, PharmD, is Associate Professor, Department of Pharmacy and Pharmaceuticals, School of Pharmacy, and Department of Internal Medicine (Nephrology), School of Medicine, at Virginia Commonwealth University. Dr. Comstock has been active in the field of renal pharmacotherapy for 17 years. His teaching, research, and patient care activities focus on the pharmacokinetics and pharmacodynamics of drugs in patients with renal impairment, with the goal of improved patient outcomes. Recent areas of research include strategies for the optimization of therapy in the treatment of anemia, and antibiotic dosing strategies during hemodialysis. He has also guided protocol development for anemia management in affiliated dialysis centers. He is an active member of the American College of Clinical Pharmacy - Nephrology Practice Research Network and other pharmacy and nephrology organizations, and serves on the nephrology editorial panel for the *Annals of Pharmacotherapy.*

Kathy Jabs, MD, is the Director of Pediatric Nephrology at Vanderbilt University Medical Center and an Associate Professor of Pediatrics at Vanderbilt University School of Medicine, Nashville, TN. Dr. Jabs has had a long-standing interest in the care of children with chronic kidney disease. Her clinical and research interests have included evaluations of the outcomes of dialysis and transplantation in children as well as the factors contributing to morbidity in these children, such as anemia and growth retardation. Dr. Jabs has published and given invited lectures on these topics. She is currently a member of the Scientific Advisory Committee of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). Dr. Jabs is a member of the speaker's bureau for Schein Pharmaceuticals.

J. Michael Lazarus, MD, is Senior Vice President of Clinical Quality and Medical Director of Fresenius Medical Care North America. Dr. Lazarus has been affiliated with Fresenius Medical Care North America (formerly National Medical Care, Inc.) for 25 years as a Medical Director and consultant. Dr. Lazarus is Vice Chairman of the Board of Directors of Renaissance Health Care Inc. and is on the Board of Directors of Optimal Health Care, Inc. Dr. Lazarus received his undergraduate degree from the University of North Carolina and his medical degree from Tulane University. His internship and residency training were at Emory University/ Grady Hospital and Tulane University/ Charity Hospital. Dr. Lazarus completed his nephrology training at Harvard Medical School and the Peter Bent Brigham Hospital. Prior to assuming his present position at FMCNA in April, 1996, Dr. Lazarus was Director of Clinical Services in the Nephrology Division and Director of the Dialysis Unit at the Brigham and Women's Hospital and continues to hold the position of Associate Professor of Medicine at Harvard Medical School.

Allen Nissenson, MD, is a Professor of Medicine at the University of California, Los Angeles,

and Director of the Dialysis Program. After completing a 2-year fellowship in nephrology at Northwestern University Medical School, Dr. Nissenson was recruited to UCLA in 1977, where he developed a comprehensive dialysis program. Dr. Nissenson has served as Chair of the Southern California End Stage Renal Disease (ESRD) Network, and is currently Chair of the Medical Advisory Board of the NKF of Southern California. He has long been concerned with issues of healthcare delivery and has consulted for Rand Corporation on ESRD reimbursement and Baxter Healthcare Corporation on peritoneal dialysis. He is currently working with Renal management Strategies (RMS) and RMS Lifeline to develop renal disease management and outpatient vascular access care programs. Dr. Nissenson has served as Chair of the Quality Assurance Committee of the Forum of ESRD Networks, and the Council on Dialysis of the NKF, and is a member of the board and President of the Renal Physicians Association. He was a Robert Wood Johnson Health Policy Fellow of the Institute of Medicine, serving in the office of Senator Paul Wellstone. Dr. Nissenson is the author of numerous scientific papers related to clinical aspects of the care of dialysis patients, and is the editor of two dialysis textbooks. He was the founding editor-in-chief of *Advances in Renal Replacement Therapy.*

John Stivelman, MD, is Chief Medical Officer of the Northwest Kidney Centers, and Associate Professor of Medicine in the Division of Nephrology, Department of Medicine, at the University of Washington School of Medicine in Seattle. Dr. Stivelman has been involved in investigative efforts to optimize hematopoietic therapy for dialysis patients since recombinant erythropoietin was used in phase III human trials in 1986. His major interests center on iron utilization, mechanisms of resistance to erythropoietin therapy, and factors that improve dialytic survival of disadvantaged populations. Dr. Stivelman also serves as medical director of one of the Northwest Kidney Centers' freestanding facilities. He has served previously as the chair of the Network 6 Medical Review Board, as a member of the Forum of Networks Board of Directors and CQI Committee, and the MKSAP for Nephrology.

David Van Wyck, MD, is Professor of Medicine and Surgery at the University of Arizona College of Medicine. He has an active Nephrology practice at Tucson Associates in Nephrology-Hypertension. An investigator for more than 25 years, he has published and spoken widely on anemia and anemia management in patients with chronic kidney disease. He has led or participated in sentinel clinical trials in his field, beginning with the US Phase III Epoetin alfa trials. He has served as Chief of the Renal Section at the Arizona Health Sciences Center, Medical Director of the University-affiliated Desert Dialysis Center, Chief of Medicine at the Tucson VA Medical Center, coordinator of medical student and residency training programs at the VA Medical Center, and is a member of the Arizona Kidney Foundation Medical Advisory Board.