Treatment of Anemia in CKD Patients

Dr. Shahram Taheri

CKD is a worldwide public health issue.

The incidence and prevalence of kidney failure are increasing, outcomes are poor, and the cost is high.

The prevalence of earlier stages of CKD is approximately 100 times greater than the prevalence of kidney failure, affecting almost 11% of adults.

There is growing evidence that some of the adverse outcomes of CKD can be prevented or delayed by preventive measures, early detection, and treatment.

Strategies to improve outcomes include Clinical Practice Guidelines (CPGs) for CKD and for the management of hypertension, dyslipidemia, bone disease, nutrition, and cardiovascular disease (CVD) in patients with CKD.

Anemia commonly contributes to poor quality of life (QOL) in patients with chronic kidney disease (CKD).

Fortunately, among the disorders that may afflict patients with CKD, anemia is perhaps the most responsive to treatment.

Anemia is the clinical manifestation of a decrease in circulating red blood cell mass and usually is detected by low blood hemoglobin (Hb) concentration.

The cause, treatment, and prognostic significance of anemic disorders vary widely.

Causes are distinguished clinically by markers of the magnitude and appropriateness of a marrow response to anemia.

Effective circulating red blood cell mass is controlled by specialized interstitial cells in the kidney cortex that are exquisitely sensitive to small changes in tissue oxygenation.

If tissue oxygenation decreases because of anemia or other causes, these cells sense hypoxia and produce erythropoietin.

Within erythroid islands, the autonomous unit of erythropoiesis in marrow, receptors on the surface of the earliest red blood cell progenitors, erythroid colony-forming units (CFU-Es), bind erythropoietin.

Binding of erythropoietin to erythropoietin receptors salvages CFU-Es and the subsequent earliest erythroblast generations from preprogrammed cell death (apoptosis), thereby permitting cell survival and division and the eventual expansion of erythropoiesis.

If successful, these erythropoietin-stimulated events increase the production of reticulocytes, restore normal circulating red blood cell mass, and correct tissue hypoxia.

IDENTIFYING PATIENTS AND INITIATING EVALUATION

Identifying anemia is the first step in evaluating the prognostic, diagnostic, and therapeutic significance of anemia in the patient with CKD.

Haemoglobin cut offs in general population

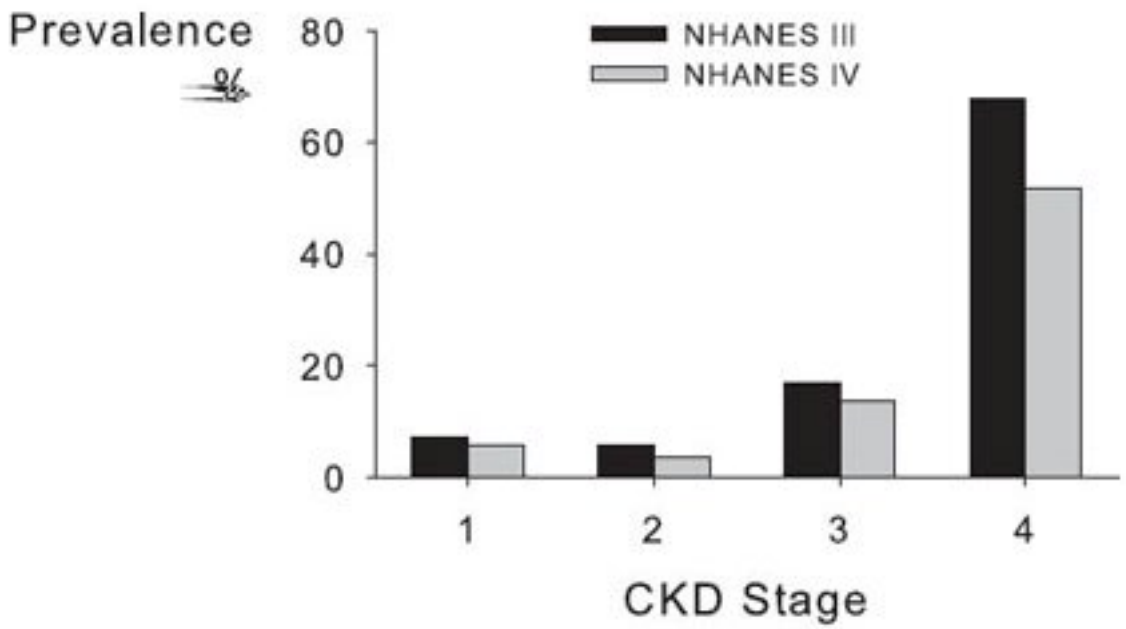
defining anaemia in people living at sea level

Age or gender group	Haemoglobin below (g/dl)
Children	
6 months to 5 years	11.0
5 to 11 years	11.5
12 to 14 years	12.0
Non-pregnant females > 15 years	12.0
Males > 15 years	13.0

Anemia has been defined by the World Health Organization (WHO) as a hemoglobin (Hgb) concentration below 13.0 g/dL for adult males and post-menopausal women, and an Hgb below 12.0 g/dL for premenopausal women.

Based upon these criteria, nearly 90 percent of patients with a glomerular filtration rate (GFR) less than 25 to 30 mL/min have anemia, many with Hgb levels below 10 g/dL.

Prevalence of anemia by CKD stage.



renal anaemia

damaged kidney

↓

impaired production of erythropoietin

↓

reduced number of red blood cells

↓

anaemia

Red Blood Cell

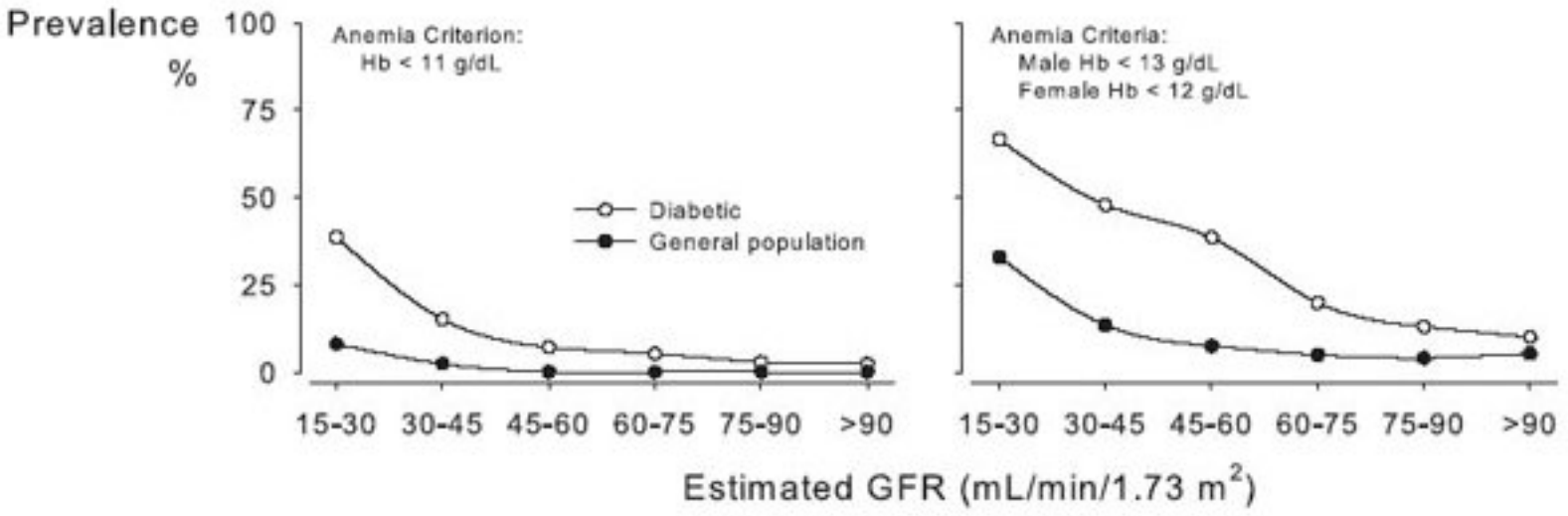
Other causes of anaemia in CKD

chronic blood loss
iron deficiency
vitamin B_{12} or folate deficiency
hypothyroidism
chronic infection or inflammation
hyperparathyroidism
aluminium toxicity
malignancy
haemolysis
bone marrow infiltration
pure red cell aplasia

Patients with diabetes are more prone to both develop anemia and develop anemia at earlier stages of CKD than their nondiabetic counterparts.

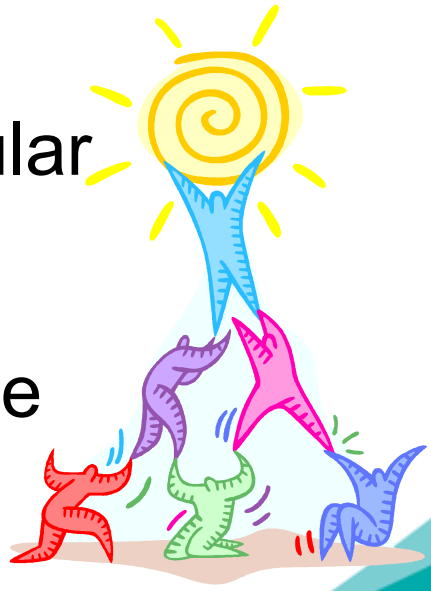
In a cross-sectional clinical audit of 820 Australian patients with diabetes, anemia was 2 to 3 times more prevalent in patients with diabetes compared with the general population at all levels of GFR.

Prevalence of low Hb level by eGFR in patients with diabetes compared with the general population.



Key goals in managing anaemia of CKD

- increase exercise capacity
- improve cognitive function
- regulate and/or prevent left ventricular hypertrophy
- prevent progression of renal disease
- reduce risk of hospitalisation
- decrease mortality



IDENTIFYING PATIENTS AND INITIATING EVALUATION

Anemia develops early in the course of CKD and is nearly universal in patients with CKD stage 5.

The purpose of specifying Hb level thresholds to define anemia is to identify patients who are most likely to show pathological processes contributing to a low Hb level and who therefore are most likely to benefit from further anemia evaluation.

Frequency of Hb Testing in Patients With CKD

Hb levels should be measured at least annually.

Because little is known about the natural history of anemia in patients with CKD, precise information is unavailable to determine the optimum frequency of Hb testing in patients with CKD.

The recommendation that patients be evaluated at least annually rests on observations from clinical trials that (in the absence of ESA therapy) the natural history of anemia in patients with CKD is a gradual decline in Hb levels over time.

Diagnosis of Anemia

Diagnosis of anemia should be made and further evaluation should be undertaken at Hb concentrations less than 13.5 g/dL in adult males and less than 12.0 g/dL in adult females.

The recommended thresholds for defining anemia represent the mean Hb of the lowest fifth percentile of the sex-specific general adult population.

If untreated, the hematocrit of patients with advanced chronic kidney disease normally stabilizes at approximately 25 percent in the absence of bleeding or hemolysis.

Table 1. Key Differences between Current Guidelines (KDOQI Anemia 2006) and Previous Anemia Guidelines (KDOQI 2000 and EBPG 2004)

Topic	KDOQI 2000 Anemia Guideline	EBPG 2004 Anaemia Guideline	KDOQI 2006 Anemia Guideline	Reason KDOQI 2006 Differs from Prior Guidelines
Definition of Anemia by Hb	<12.0 g/dL in males and postmenopausal females <11.0 g/dL in premenopausal females and prepubertal patients	<12.0 g/dL males <11.0 g/dL females	<13.5 g/dL males <12.0 g/dL females	KDOQI 2006 uses more recent NHANES data set, defines anemia as any Hb below the 5th percentile for the adult, gender-specific population. Among males, no adjustment is made for age >70 years, to exclude the possibility that pathological conditions contribute to lower Hb values. Among females, the 5th percentile determination is made only among individuals without evidence of iron deficiency, as defined by TSAT <16% or ferritin <25 ng/mL.
Target Hb	11-12 g/dL	>11.0 g/dL target >12.0 in CVD not recommended Hb >14.0 g/dL not desirable	≥11 g/dL, caution when intentionally maintaining Hb >13 g/dL	Current guideline reflects QOL benefits at Hb maintained ≥11.0 g/dL, risks when intentionally maintaining Hb >13.0, and recognition that Hb will often exceed 13 g/dL unintentionally, without evidence of increased risk, in patients with Hb intent to treat ≥11.0 g/dL.
Target Iron Status	TSAT (%) lower limit: 20 upper limit: 50 Ferritin (ng/mL) lower limit: 100	TSAT (%) lower limit: 20 target: 30-50 Ferritin (ng/mL) lower limit: 100 target: 200-500	TSAT (%) lower limit ≥20 Ferritin (ng/mL) lower limit: 200 HD-CKD 100 non-HD-CKD > 500 not routinely recommended	TSAT: Current guideline reflects unchanged lower bound for iron therapy; upper limit of TSAT not specified. Ferritin: Current guideline distinguishes HD- from non-HD-CKD on basis of available evidence. Lower limit sets objective of iron therapy. There is insufficient evidence to assess harm and benefit in maintaining ferritin > 500 ng/mL . In HD-CKD, 200 ng/mL reflects evidence for substantial efficacy of IV iron at ferritin <200 ng/mL.
Adjuvants				
L-Carnitine	Not recommended	Not recommended for general use	Not routinely recommended	Current guideline based on low-quality evidence which shows lack of efficacy
Ascorbate			Not routinely recommended	Current guideline reflects combination of safety concerns and low quality evidence of efficacy
Androgens		Selective use	Not recommended	Current guideline reflects serious safety concerns. Evidence for efficacy is low quality.

Initial assessment of anemia

The anemia observed with chronic kidney disease is largely diagnosed by excluding non-renal causes of anemia in the patient with a suitably decreased GFR.

Initial assessment of anemia

The evaluation of patients should therefore include red blood cell indices, absolute reticulocyte count, serum iron, total iron binding capacity, percent transferrin saturation, serum ferritin, white blood cell count and differential, platelet count, and testing for blood in stool. The content of hemoglobin in reticulocytes can also be assessed.

This work-up should be performed prior to administering ESA therapy.

Evaluating Iron Status in Anemic Patients With CKD

Iron status test results reflect either the level of iron in tissue stores or the adequacy of iron for erythropoiesis.

Serum ferritin level is the only available blood marker of storage iron.

Tests that reflect adequacy of iron for erythropoiesis include TSAT, MCV, and MCH and the related indices, percentage of hypochromic red blood cells (PHRC) and content of Hb in reticulocytes (CHr).

Absolute iron deficiency is likely to be present in patients with end-stage renal disease when:

The percent transferrin saturation (plasma iron divided by total iron binding capacity x 100, TSAT) falls below 20 percent.

The serum ferritin concentration is less than 100 ng/mL among predialysis and peritoneal dialysis patients or is less than 200 ng/mL among hemodialysis patients.

This difference in the serum ferritin level is based upon accumulating evidence in hemodialysis patients that the maintenance of ferritin levels above 200 ng/mL is associated with decreased erythropoietin requirements.

By comparison, when a patient with normal renal function develops severe anemia due to iron deficiency, the serum ferritin concentration is typically below 30 ng/mL.

The discrepancy between subjects with normal renal function and those with end-stage renal disease with respect to the serum ferritin concentration may in part reflect an underlying inflammatory state associated with advanced renal failure and dialysis.

	Normal	Fe deficiency without anemia	Fe deficiency with mild anemia	Severe Fe deficiency with severe anemia
Marrow reticulo-endothelial iron	**2+ to 3+**	**None**	None	None
Serum iron (SI), µg/dL	60 to 150	60 to 150	**<60**	<40
Total iron binding capacity (transferrin, TIBC), µg/dL	300 to 360	300 to 390	350 to 400	**>410**
Transferrin saturation (SI/TIBC), percent	20 to 50	30	**<15**	<10
Hemoglobin, g/dL	**Normal**	**Normal**	**9 to 12**	**6 to 7**
Red cell morphology	Normal	Normal	Normal or slight hypochromia	Hypochromia and microcytosis
Plasma or serum ferritin, ng/mL	40 to 200	**<40**	<20	<10
Erythrocyte protoporphyrin, ng/mL RBC	30 to 70	30 to 70	**>100**	100 to 200
Other tissue changes	None	None	None	Nail and epithelial changes

Laboratory tests in iron deficiency of increasing severity

	Sensitivity (percent)	Specificity (percent)
Transferrin saturation (percent)		
<15	16	88
<18	58	75
<21	81	63
<24	88	44
<27	92	22
<30	96	11
Serum ferritin (ng/mL)		
<50	37	75
<100	48	75
<150	71	69
<200	77	37
<300	90	18
<500	100	0

Accuracy of serum ferritin and transferrin saturation in the diagnosis of functional iron deficiency among dialysis patients.

Functional iron deficiency

Functional iron deficiency is characterized by the presence of adequate iron stores, but an inability to sufficiently mobilize this iron to adequately support erythropoiesis with the administration of EPO.

The serum ferritin level is either normal or markedly elevated, but the transferrin saturation typically falls to about 20 percent or below.

Functional iron deficiency, which usually responds somewhat to iron therapy, must be distinguished from inflammatory iron block, which usually does not.

Inflammatory iron block occurs among patients with refractory anemia due largely to an underlying inflammatory state.

Both functional deficiency and inflammatory block are associated with transferrin saturation ≤20 percent and elevated ferritin level (between 100 to 800 ng/mL or even higher.

The response to EPO and/or parenteral iron may help distinguish between functional iron deficiency and inflammatory block.

Monitoring Iron Store

Monitoring serum ferritin levels and the percent transferrin saturation every three months is probably adequate in patients with adequate iron stores who are on maintenance oral or intravenous iron, especially after the first few months when iron stores are most likely to become depleted.

By comparison, monitoring every one to two months is recommended in patients just starting EPO therapy or in whom the dose has been increased, in those with marginal iron status, or in those patients with declining serum ferritin or TSAT levels.

Upper Level of Ferritin

There is insufficient evidence to recommend routine administration of IV iron if ferritin level if greater than 500 ng/mL reflects the findings of the Work Group that:

(1)- no RCTs have compared the safety and efficacy of ferritin targets greater than 500 ng/mL with the safety and efficacy of lower ferritin targets,

(2)- few studies have examined the efficacy of IV iron at ferritin levels greater than 500 ng/mL,

(3)- no study has examined either efficacy or safety beyond surrogate outcomes,

(4)- no information from interventional trials is available about the safety of ferritin targets greater than 500 ng/mL,

(5)- sufficient evidence exists to suggest that tissue iron stores in patients with ferritin levels greater than 500 ng/mL are normal to greater than normal.

Route of Administration

The preferred route of iron administration is IV in patients with HD-CKD

The route of iron administration can be either IV or oral in patients with ND-CKD and PD-CKD

The 2006 K/DOQI guidelines suggest that oral iron should be administered at a daily dose of at least 200 mg of elemental iron.

The simplest and least expensive formulation to achieve this is ferrous sulfate 325 mg (65 mg elemental iron per tablet) three times daily.

Intestinal iron absorption is intrinsically normal in renal failure, but may be reduced by food and antacids.

Thus, oral iron should be given between meals, if tolerated.

Giving one of the doses at bedtime may be a simple and effective expedient.

Because of the decreased efficacy and other adverse factors associated with traditional oral iron, a new generation of oral iron products have been developed.

For example, heme iron polypeptide is absorbed in the gastrointestinal tract via different mechanisms from nonheme iron, resulting in absorption kinetics and side effects that differ from traditional iron products.

In a six-month prospective trial of hemodialysis patients, heme iron polypeptide adequately maintained both hemoglobin levels and serum iron indices after substituting for intravenous iron.

Although further study is needed, these results suggest that this oral formulation may become a viable option for iron delivery.

Erythropoietin Therapy

Selection of the Hb target and selection of the Hb level at which ESA therapy is initiated in the individual patient should include consideration of potential benefits (including improvement in quality of life and avoidance of transfusion) and potential harms (including the risk of life-threatening adverse events).

Whom to treat and target hemoglobin level

Patients with chronic renal failure not on dialysis and dialysis patients should have a hemoglobin level less than 10 g/dL prior to starting treatment.

In dialysis and nondialysis patients with CKD receiving ESA therapy, the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL.

Whom to treat and target hemoglobin level

In dialysis and nondialysis patients with CKD receiving ESA therapy, the Hb target should not be greater than 13.0 g/dL.

Dose

The initial ESA dose and ESA dose adjustments should be determined by the patient's Hb level, the target Hb level, the observed rate of increase in Hb level, and clinical circumstances.

The initial EPO dose should be approximately 50 to 100 units/kg per week.

In patients with chronic kidney disease who are not on dialysis, EPO is commonly given only once per week (or less frequently).

Because of patient convenience and the need to preserve veins for future hemodialysis access, EPO be administered subcutaneously in this setting.

In practice, most patients are dosed by unit dosing (eg, a vial), rather than on a units/kg basis. Thus, therapy in most patients begin at 10,000 units subcutaneously once weekly or 20,000 units subcutaneously every other week.

In general, the objective of initial ESA therapy is a rate of increase in Hb levels of 1 to 2 g/dL per month.

However, the use of lower doses would also be reasonable, particularly in patients with pretreatment Hgb levels near 11 g/dL.

If necessary, subsequent adjustments are made in interval and/or dose.

Higher doses given less frequently have also been used, although the long-term safety and benefit of this approach are not known.

Monitoring

Monitoring of the hemoglobin level every two to four weeks is recommended, which is commonly used in practice; however, current recommendations from the FDA are for more frequent testing.

Side effects

The most common side effects of EPO treatment, aside from hypertension and its related problems, are headache (which occurs in 15 percent of cases) and an influenza-like syndrome (affecting 5 percent).

The influenza-like syndrome is of unknown etiology, but is responsive to anti-inflammatory drugs.

Adverse cardiovascular effects have been associated with targeting hemoglobin levels that are higher than 13 g/dL.

Pure red cell aplasia — Among patients administered rHuEPO subcutaneously, the development of pure red cell aplasia has been described in association with the presence of neutralizing anti-erythropoietin antibodies.

Hyporesponsiveness to EPO

Some patients are relatively resistant to EPO and require large doses.

This may be an important clinical observation since a poor response to EPO therapy may be associated with increased mortality.

Higher doses of EPO have also been associated with an increased mortality, an effect that persists after adjustment for the usually lower hematocrit in such patients

A large EPO requirement is defined as either the requirement of excessive doses during initiation of therapy, or inability to achieve or maintain target Hgb levels despite the large dose in the iron-replete patient. Different guidelines have suggested different definitions:

450 U/kg per week intravenous EPO or 300 U/kg per week subcutaneous EPO, per K/DOQI

300 U/kg per week of EPO (approximately 20,000 U/week) and 1.5 mcg/kg per week of darbepoetin alfa (approximately 100 mcg/week), per the revised European Guidelines.

The most common cause of resistance to EPO is absolute iron deficiency which may be due to external blood losses and/or exhaustion of iron stores due to an increase in erythropoiesis caused by EPO treatment.

Patients with functional iron deficiency may also respond to supplemental iron administration with an increase in hemoglobin level and/or reduction in EPO dose.

Additional causes include the following:

Bone disease due to secondary hyperparathyroidism; this should be suspected when EPO resistance occurs in iron replete patients in the setting of severe hyperparathyroidism.

Occult malignancy and unsuspected hematologic disorders.

Multiple myeloma/myelofibrosis/myelodysplastic syndrome.

Chronic inflammation (with inhibition possibly due to enhanced cytokine production).

The presence of a failed kidney transplant or an occult infection of an old nonfunctioning arteriovenous graft may underlie such inflammation in some patients, with removal or resection frequently resolving resistance.

This is also consistent with the observation that an increased number of vascular access related infections and dialysis catheter insertions is associated with higher EPO requirements.

Although now rare, the accumulation of aluminum in bone.

Hemoglobinopathies, as patients with sickle cell disease or trait may have an inadequate response to the administration of EPO.

The administration of angiotensin converting enzyme inhibitors and/or angiotensin II receptor antagonists.

Some reports, but not all, suggest that these agents may result in relative EPO resistance.

Development of pure red cell aplasia associated with the presence of neutralizing anti-erythropoietin antibodies in patients treated with particular brands of EPO by the subcutaneous route.

Presence of HIV infection.