Anemia of Chronic Kidney Disease

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Chronic Kidney Disease (CKD)

- National Kidney Foundation (NKF) classification system 2002 for staging CKD
- CKD previously called:
  - Chronic renal failure
  - Pre-ESRD (End Stage Renal Disease)
  - Renal failure
  - Renal damage
  - Kidney disease
KDOQI Defines CKD

**Kidney Disease Outcomes Quality Initiative**

- KDOQI defines CKD according to the presence or absence of markers of kidney damage and the level of kidney function (GFR) – irrespective of the type of kidney disease (the specific diagnosis).
- Thus, there are two independent criteria for CKD:

**Table 11. Definition of Chronic Kidney Disease**

<table>
<thead>
<tr>
<th>Criteria</th>
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</thead>
<tbody>
<tr>
<td>1. Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by <em>either</em>:</td>
</tr>
<tr>
<td>• Pathological abnormalities; or</td>
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<tr>
<td>• Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests</td>
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<tr>
<td>2. GFR &lt;60 mL/min/1.73 m² for ≥3 months, with or without kidney damage</td>
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</table>

Methods to estimate GFR are discussed in Guideline 4. Markers of kidney damage are discussed in Guidelines 5–6.

# Stages of Chronic Kidney Disease

NKF Kidney Disease Outcomes Quality Initiative (K/DOQI): CKD Stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or ↑ GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild ↓ GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 (or dialysis)</td>
</tr>
</tbody>
</table>

NKF-K/DOQI Stages of CKD

**CKD Continuum**

**Renal Insufficiency**

1. Kidney Damage with normal or ↑ GFR
2. Kidney Damage with Mild GFR ↓
3. Moderate GFR ↓
4. Severe GFR ↓
5. Kidney Failure

![GFR (mL/min/1.73 m²)]

<15 or Dialysis/Transplantation (RRT)

Anemia
Anemia is one of the most common manifestations of CKD.

Untreated anemia can, depending on its severity, be associated with a number of abnormalities:

- Decreased oxygen delivery to the tissues
- Increased cardiac output and cardiomegaly;
- Decreased cognition and mental acuity; and
- Overall decrease in patient welfare
Defining Anemia (NKF)

- Group of diseases characterized by a decrease in either Hb, Hct or RBC that reduce the oxygen carrying capacity of the blood.

Diagnose anemia if:
- Hb < 12 g/dL (adult females)
- Hb < 13.5 g/dL (adult males)

- In patients with CKD the hemoglobin should be 11 g/dL or greater

**World Health Organization**

- **WHO definition of anemia:**
  - Males \( \text{Hgb} < 13 \text{ gm/dL} \)
  - Females \( \text{Hgb} < 12 \text{ gm/dL} \)

Cause of Anemia in Long Term Care

- Chronic disease: 65.6%
- CKD: 13.2%
- Unknown: 15.9%
- Fe, B₁₂, folate: 4.0%
- Other: 1.3%

LTC = long-term care.

Signs and Symptoms of Anemia Are Nonspecific

Central nervous system (CNS)
- Fatigue
- Headache
- Dizziness
- Syncope
- Depression
- Impaired cognition

Cardiorespiratory system
- Dyspnea
- Tachycardia
- Systolic ejection murmur
- Palpitations
- Cardiac enlargement
- Hypertrophy
- Wide pulse pressure
- Hypotension
- Orthostasis

Vascular system
- Cold intolerance
- Edema
- Pallor of skin, mucous membranes, and conjunctivae

Gastrointestinal system
- Anorexia
- Nausea

Genital tract
- Impotence

Adverse Outcomes Associated With Anemia in Older Adults

- Decreased muscle strength and physical function
- Increased risk of stroke
- Increased frequency of hospital admission and death
- Cognitive impairment
- Increased heart disease
- Increased falls and fall-related injuries

References:
Anemia of CKD
Anemia Prevalence by CKD Stage

*NHANES participants aged ≥20 y with anemia as defined by WHO criteria: hemoglobin (Hgb) <12 g/dL for women, and Hgb <13 g/dL for men.

USRDS 2004 Annual Data Report. The data reported here have been supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government. Available at: www.usrds.org. Accessed 3/28/05.

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Anemia Worsens as Kidney Function Declines

Hb Levels
- Hb=11-12 g/dL (n=181)
- Hb=10-11 g/dL (n=105)
- Hb=<10 g/dL (n=315)

Prevalence of Anemia (%) vs. Serum Creatinine Level (mg/dL)

Etiology and Pathogenesis

- The primary cause of the anemia is decreased production of EPO.

- In adults and children, EPO is produced primarily by the peritubular-interstitial cells of the kidney; therefore, the loss of functioning kidney parenchyma results in impaired EPO generation.

- Under normal conditions, circulating erythropoietin levels are low, but are augmented as much as 100- to 1000-fold in response to anemia or tissue hypoxia in a process mediated by hypoxia-inducible factor 1.

- Decreased serum iron concentration may contribute to the anemia and limit the response to exogenous EPO administration.
Erythropoietin

- Inverse correlation bet. EPO & rbc mass
- EPO immunoassay, two – site ELISA
- WHO calibrated Standard
- Specimen: Serum
- The best time: 7:30 AM - 12:00 noon, Diurnal variation
- Blood should be clotted at 2-8\(^\circ\)C, if clotted at RT may decrease up to 30%
- Avoid grossly hemolyzed or grossly lipemic sample
- RI: 3.22-31.9 mIU/ml
Common pathogenic mechanisms for anemia of CKD/ESRD

- Patients with CKD/ESRD may develop anemia on the basis of any etiology, including:
  - Vitamin B12 and folic acid deficiency,
  - inherited hemoglobinopathy,
  - bleeding,
  - hemolysis,
  - medications,
  - malignancy,
  - and bone marrow infiltration.
Factors That Cause or Contribute to Anemia in CKD

- Erythropoietin deficiency (insufficient production of endogenous erythropoietin)
- Iron deficiency
- Acute/chronic inflammatory conditions
- Severe hyperparathyroidism
- Aluminum toxicity
- Folate deficiency
- Decreased RBC survival
- Hemoglobinopathies (e.g., alpha-thalassemia, sickle-cell anemia)

Common pathogenic mechanisms for anemia of CKD/ESRD

- Loss of kidney parenchyma
  - Hyperparathyroidism
- Decreased erythropoietin production
- Blood loss:
  - Dialytic
  - GI
  - Phlebotomy
  - Other
- Erythropoietin/ESA:
  - Hyporesponsiveness
  - Resistance
- Iron deficiency:
  - Absolute
  - Functional
- Anemia
- Hospitalization
- Inflammation/infection
- Poor nutrition
- Retained uremic solutes

ESA: Erythropoietic Stimulating Agent
CHRONIC KIDNEY DISEASE

EPO defic.  Iron defic.  Erythropoiesis suppr.  Inflammation  Oxidative stress

ANEMIA

Hemolysis  Vitamin defic.  Malnutrition  HyperPTH  Aluminum ?  ACEI

CHRONIC KIDNEY DISEASE
Healthy RBC Production Requires EPO and Iron

Erythropoietin levels are not routinely used in distinguishing erythropoietin deficiency from other causes of anemia in patients with CKD in most clinical settings and their measurement is generally not recommended.

Approach to normocytic anemia

normocytic anemia

Is there increased red cell production?

check reticulocyte count

increased

Is there evidence of:  
- renal failure  
- endocrine failure  
- chronic inflammation

anemia of renal failure

normal or decreased

Is there evidence of hemolysis?

yes

hemolytic anemia

no

recent bleed

consider

bone marrow failure

bone marrow investigation
Evaluation of Anemia

- Complete blood count
- Erythrocyte indices
- Reticulocyte count
- Iron parameters
- CRP
- Stool occult blood
- Vitamin B 12, folate, copper
- PTH
- Serum ferritin
- Transferrin saturation
- Reticulocyte Hb content
- Hypochromic RBC
- Hemolysis
A step-by-step guide to CKD anemia diagnosis and treatment

Serum creatinine ≥2 mg/dL
Male and postmenopausal female hemoglobin <12 g/dL
Premenopausal female hemoglobin <11 g/dL

Iron deficient
- CBC with differential
- Ferritin
- TIBC/TSAT
- Reticulocyte
- B12
- Folate
- Stool guaiac
- Serum Fe

B12/folate deficient
- Supplement B12/folate

R/O occult GI malignancy

No malignancy

Corrected

Initiate iron therapy

Adequate iron stores

Start ESA if hemoglobin <10 g/dL
Monitor iron stores periodically

Unclear/malignancy
- Referral to hematology

CBC, complete blood count; CKD, chronic kidney disease; ESA, erythropoietin-stimulating agents; R/O, rule out; TIBC/TSAT, total iron-binding capacity/transferrin saturation.
Diagnosis of anemia

- Diagnose anemia in adults and children >15 years with CKD when the Hb concentration is <13.0 g/dl (<130 g/l) in males and <12.0 g/dl (<120 g/l) in females. (Not Graded)
- Diagnose anemia in children with CKD if Hb concentration is:
  - <11.0 g/dl (<110 g/l) in children 0.5–5 years,
  - <11.5 g/dl (115 g/l) in children 5–12 years, and
  - <12.0 g/dl (120 g/l) in children 12–15 years. (Not Graded)
Assessment of Anemia in CKD

- **Test Hb at least annually in all patients, regardless of stage or cause of CKD**
  
  Hct is a derived value, affected by plasma water, and, therefore, can be imprecise as a direct assessment of erythropoiesis. In contrast to Hct, Hb values are absolute and directly impacted by decreased erythropoietin production by the kidney

- **Assessment should include the following tests:**
  - A complete blood count
  - Absolute reticulocyte count
  - Serum ferritin to assess iron stores
  - Serum transferrin saturation (TSAT) or content of Hb in reticulocytes to assess adequacy of iron for erythropoiesis
  - Stool for occult blood

Ecchinocyte & spiculated rbc
Ecchinocytes
Frequency of testing for anemia

- For CKD patients **without anemia** measure Hb concentration when clinically indicated and (Not Graded):
  - At least **annually** in patients with CKD 3
  - At least **twice per year** in patients with CKD 4–5 ND
  - At least **every 3 months** in patients with CKD 5HD and CKD 5PD

<table>
<thead>
<tr>
<th>CKD Categories</th>
<th>Definition</th>
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<tbody>
<tr>
<td>CKD</td>
<td>CKD of any stage (1-5), with or without a kidney transplant, including both non-dialysis dependent CKD (CKD 1-5ND) and dialysis-dependent CKD (CKD 5D)</td>
</tr>
<tr>
<td>CKD ND</td>
<td>Non-dialysis-dependent CKD of any stage (1-5), with or without a kidney transplant (i.e., CKD excluding CKD 5D)</td>
</tr>
<tr>
<td>CKD T</td>
<td>Non-dialysis-dependent CKD of any stage (1-5) with a kidney transplant</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specific CKD Stages</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD 1, 2, 3, 4</td>
<td>Specific stages of CKD, CKD ND, or CKD T</td>
</tr>
<tr>
<td>CKD 3-4, etc.</td>
<td>Range of specific stages (e.g., both CKD 3 and CKD 4)</td>
</tr>
<tr>
<td>CKD 5D</td>
<td>Dialysis-dependent CKD 5</td>
</tr>
<tr>
<td>CKD 5HD</td>
<td>Hemodialysis-dependent CKD 5</td>
</tr>
<tr>
<td>CKD 5PD</td>
<td>Peritoneal dialysis-dependent CKD 5</td>
</tr>
</tbody>
</table>
Frequency of testing for anemia

- For CKD patients with anemia not being treated with an ESA, measure Hb concentration when clinically indicated and (Not Graded):
  - At least every 3 months in patients with CKD 3–5ND and CKD 5PD
  - At least monthly in patients with CKD 5HD
Diagnostic and monitoring considerations

- Iron stores should be reassessed 1-2 months following the initiation of ESA therapy because brisk erythropoiesis rapidly consumes body iron stores and repletion should be administered as indicated.

- Once Hb levels, ESA dose, and iron stores have stabilized, iron monitoring can be spaced out to every 3 months, but more frequent monitoring is indicated when Hb levels fall, ESA dose requirements rise, or iron stores become marginal.

- In hemodialysis patients, more frequent monitoring may be indicated given the frequent blood loss incurred.
Dietary restrictions
Anorexia

Malnutrition
Inflammation
Phosphate binders

Decrease in oral iron intake

Blood loss in HD
Blood sampling
GI bleeding

Decrease in intestinal Iron absorption

IRON DEFICIENCY

Stimulation of erythropoiesis by ESA

Chronic blood loss

erythropoiesis-stimulating agent (ESA) therapy
Functional iron deficiency is defined as the presence of adequate bone marrow iron stores, but an impaired ability to mobilize these stores for erythropoiesis in the presence of the stimulating effect of an ESA.
Hepcidin Regulates Cellular Iron Export Into Plasma

Low hepcidin

Iron uptake

Iron-exporting cells (duodenal enterocytes, macrophages, hepatocytes)

ferritin

Fpn

Fe

Iron release into plasma

High hepcidin

Iron uptake

ferritin

Fpn

Fe

hepcidin

Hepcidin as the Main Regulator of Systemic Iron Homeostasis

Hb testing in all patients with CKD at least annually

Hb < 13.5 g/dl, adult males, or Hb < 12 g/dl, adult females

Diagnosis of anemia

- CBC + RBC indexes to assess anemia severity, adequacy of nutrients such as vitamin B₁₂, folate, iron
- Absolute reticulocyte count (corrected for Hb value) to assess erythropoietic activity

Normochromic, normocytic CKD

Start/adjust ESA based on Hb

ESA monitoring
Monitor Hb weekly after initiating ESA until stable and then at least monthly

Adjust ESA no more frequently than every 4 weeks, unless clinically indicated (unstable Hb, bleeding, surgery, hospitalization)

Macrocytic
Vitamin B₁₂ and/or folate deficiency

Start renal multivitamin (water-soluble vitamins)

HD
ferritin ≤ 200 ng/ml and
TSAT ≤ 20% or
CHr < 99 pg/cell

Iron monitoring
Monitor monthly during initial ESA therapy, then at least every 3 months during stable ESA therapy. Monitor more frequently following blood loss, surgery, hospitalization, or after a course of IV iron

Microcytic
Iron deficiency, aluminum overload

PD or nondialysis CKD
ferritin ≤ 100 ng/ml and
TSAT ≤ 20%

Parenteral iron
Oral iron, IV iron, if necessary

Consider maintenance iron therapy in patients on HD
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
Treatment for Anemia of CKD

- Replete iron stores to maintain:
  - TSAT ≥ 20% and
  - Serum ferritin ≥ 100ng/ml
- Consider erythropoiesis-stimulating agent (ESA)
- Continue to evaluate responsiveness to treatment
- When treating with ESA, avoid Hgb > 12 gm/dL
Anemia of CKD Management

- Supplement iron; most patients should receive oral iron supplement to prevent the development of iron deficiency even if iron studies are normal at initiation of therapy*

- Select ESA therapy
  - Epoetin alfa
  - Darbepoetin alfa

- Monitor Hgb, adjust dose by 25% no more frequently than monthly to reach and maintain target

The Effect of ESAs on Erythropoiesis

BFU-E  CFU-E  Normoblast  Reticulocyte

Erythropoietin response ability
Hb Target and ESAs

- Consider risk to benefit
- Hgb targets
  - 11-12 g/dL per 2007 NKF KDOQI guidelines
  - 10-12 g/dL per FDA package inserts
  - Do not exceed Hgb >12 g/dL; adjust dose as “Hb approaches 12 gm/dL”
- Monitor Hb:
  - Weekly: darbepoetin
  - Twice weekly: epoetin
Black Box Warning

Renal Failure: Patients experienced greater risk for death and serious cardiovascular events when administered ESAs to a target higher versus lower hemoglobin level in two clinical studies.

Individualize dosing to achieve and maintain a target hemoglobin within the range of 10 to 12 g/dL.

Hb maintenance algorithm
(assumes ESA therapy and maintenance i.v. iron)

Measure Hb

- Hb < 11 g/dl
  - ↑ ESA dose/frequency as per schedule unless Hb rising by 1 g/dl/month. Check Hb as per Schedule.

- Hb 11–12 g/dl
  - No change unless Hb rising by 1 g/dl/month in which case consider ESA dose adjustment

- Hb 12–15 g/dl
  - Consider stopping i.v. iron. ↓ ESA dose/frequency as per schedule unless Hb falling by more than 1 g/dl/month. Check Hb as per schedule.

- Hb > 15 g/dl
  - Stop i.v. iron. Consider stopping ESA or halve dose/frequency. Check Hb in 2 weeks.

If Hb is persistently low see poor response algorithm

Ferritin < 200 µg/l?
Hypo-responsiveness to ESAs

POTENTIAL CAUSES

- Missed doses
- Inadequate iron stores
  - Iron deficiency is present in 25-37.5% of patients and is a common cause of hyporesponse

- Drug/disease interactions
  - Remember, iron needs an acidic environment to be maximally absorbed

- B₁₂ or folate deficiencies
- Protein deficiencies
- Occult blood loss
- Infection/inflammation processes
- Coexisting medical conditions
  - Malignancies, hematological disorders
- Hemolysis

ESA Monitoring

- Hb “at regular intervals” once stabilized\textsuperscript{1,2}
- CBC with differential and platelet count regularly
- Blood pressure should be controlled adequately before initiation of therapy
- Fe studies (TSAT, ferritin) prior to and during therapy
- Serum chemistry should be checked regularly (BUN, creatinine, phosphorus, uric acid, K+)\textsuperscript{1}

Thank you, any more to discuss?