Chapter 1: Diagnosis and evaluation of anemia in CKD

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TESTING FOR ANEMIA

BACKGROUND
In any individual, anemia may be the initial laboratory sign of an underlying medical problem. Consequently, a complete blood count, including the hemoglobin (Hb) concentration, is routinely part of global health assessment in most adults, whether or not they have chronic kidney disease (CKD). In patients with CKD but stable kidney function, the appearance or progression of anemia may herald a new problem that is causing blood loss or is interfering with red cell production. The anemia should be evaluated independently of CKD stage in order to identify any reversible process contributing to the anemia. The causes of acquired anemia are myriad and too many to include in a guideline such as this. A comprehensive list of causes and the approach to diagnosis can be found in a standard textbook of medicine or hematology. The most commonly encountered reversible cause of chronic anemia or worsening anemia in CKD patients, other than anemia related directly to CKD, is iron deficiency anemia.

Frequency of testing for anemia

1.1.1: For CKD patients without anemia (as defined below in Recommendation 1.2.1 for adults and Recommendation 1.2.2 for children), 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 4–5ND
- at least every 3 months in patients with CKD 5HD and CKD 5PD

1.1.2: 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
[See Recommendations 3.12.1–3.12.3 for measurement of Hb concentration in patients being treated with ESA.]

RATIONALE
Relatively little is known about the development and progression of anemia in patients with CKD. Consequently, one cannot determine precisely the optimal frequency at which Hb levels should be monitored. The recommendation that patients with CKD be periodically evaluated for anemia rests on observations that, in the absence of use of erythropoiesis-stimulating agents (ESAs), there often is a gradual decline in Hb over time in patients with CKD as the level of glomerular filtration rate (GFR) declines, suggesting the need for regular surveillance of Hb concentration. The frequency of Hb monitoring, regardless of CKD stage, should be influenced by the Hb level (i.e., more frequent monitoring may be appropriate in patients with more severe anemia) and rate of decline in Hb level. As kidney function declines and in patients with more advanced CKD stages, the incidence and prevalence of anemia increases. Thus, in order to identify CKD patients who may need intervention with iron administration, an ESA, or even require a transfusion, more frequent monitoring of the Hb concentration will be necessary at later CKD stages.

More frequent monitoring is recommended for adult CKD 5HD and CKD 5PD patients with anemia who are not receiving an ESA; at least monthly in CKD 5HD patients and at least every 3 months in CKD 5PD patients. In CKD 5HD patients, Hb monitoring is traditionally performed prior to a mid-week hemodialysis (HD) session. While this is not essential it probably does tend to minimize Hb variability due to the longer inter-dialytic interval between the last treatment of one week and the first of the next. As in all patients, Hb testing should be performed whenever clinically indicated, such as after a major surgical procedure, hospitalization, or bleeding episode.

In the pediatric population with CKD, there is no direct evidence to recommend a different frequency of monitoring for anemia than for adults. In the Chronic Kidney Disease in Children Prospective Cohort Study (CKiD), which evaluated 340 North American children with CKD using iothalamate-determined GFR, below a GFR threshold of 43 ml/min per 1.73 m², there was a linear relationship between Hb and GFR, with Hb 0.3 g/dl (3 g/l) lower per 5 ml/min per 1.73 m² lower GFR. Above that threshold, there was a nonsignificant association of 0.1 g/dl (1 g/l) lower Hb for every 5 ml/min per 1.73 m² lower GFR. Because serum creatinine-based estimated glomerular filtration rate (eGFR) using the Schwartz formula may overestimate the true GFR in the children’s providers need to consider the potential for Hb decline and anemia even at early stages of CKD and monitor accordingly. In children with CKD 5HD and CKD 5PD, monthly monitoring for anemia is standard clinical practice.

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Diagnosis of anemia

1.2.1: 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)

1.2.2: 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)

RATIONALE
The Hb concentration values that define anemia and should lead to initiation of an evaluation for the cause of anemia are dependent on sex and age. The recommended Hb values for adults and children represent the World Health Organization (WHO) definition of anemia and establish a benchmark for anemia workup that has been applied across populations.

An alternative source for Hb concentration values that define anemia in children between 1 and 19 years is based on US National Health and Nutrition Examination Survey III (NHANES III) data from 1988–94 (Table 1). For children between birth and 24 months, the data are taken from normal reference values (Table 2).

These thresholds for diagnosis of anemia and evaluation for the causes of anemia should not be interpreted as being thresholds for treatment of anemia. Rather than relying on a single laboratory test value, in patients without an apparent cause for a low Hb level, the value should be confirmed to be below the threshold values for diagnosis of anemia prior to initiating a diagnostic work up.

Investigation of anemia

1.3: In patients with CKD and anemia (regardless of age and CKD stage), include the following tests in initial evaluation of the anemia (Not Graded):
- Complete blood count (CBC), which should include Hb concentration, red cell indices, white blood cell count and differential, and platelet count
- Absolute reticulocyte count
- Serum ferritin level
- Serum transferrin saturation (TSAT)
- Serum vitamin B12 and folate levels

RATIONALE
Complete blood count
The complete blood count (CBC) provides information about the severity of anemia and adequacy of bone marrow function. Severity of anemia is assessed best by measuring Hb

### Table 1 | Hb levels in children between 1–19 years for initiation of anemia workup

| All races/ethnic groups | Number of subjects | Mean Hb g/dl (g/l) | Standard deviation g/dl (g/l) | Anemia definition met if value is < 5th percentile g/dl (g/l) |
|-------------------------|--------------------|-------------------|-----------------------------|----------------------------------------------------------|
| Boys                    |                    |                   |                             |                                                          |
| 1 yr and over           | 12,623             | 14.7 (147)        | 1.4 (14)                    | 12.1 (121)                                               |
| 1–2 yr                  | 931                | 12.0 (120)        | 0.8 (8)                     | 10.7 (107)                                               |
| 3–5 yr                  | 1,281              | 12.4 (124)        | 0.8 (8)                     | 11.2 (112)                                               |
| 6–8 yr                  | 709                | 12.9 (129)        | 0.8 (8)                     | 11.5 (115)                                               |
| 9–11 yr                 | 773                | 13.3 (133)        | 0.8 (8)                     | 12.0 (120)                                               |
| 12–14 yr                | 540                | 14.1 (141)        | 1.1 (11)                    | 12.4 (124)                                               |
| 15–19 yr                | 836                | 15.1 (151)        | 1.0 (10)                    | 13.5 (135)                                               |
| Girls                   |                    |                   |                             |                                                          |
| 1 yr and over           | 13,749             | 13.2 (132)        | 1.1 (11)                    | 11.4 (114)                                               |
| 1–2 yr                  | 858                | 12.0 (120)        | 0.8 (8)                     | 10.8 (108)                                               |
| 3–5 yr                  | 1,337              | 12.4 (124)        | 0.8 (8)                     | 11.1 (111)                                               |
| 6–8 yr                  | 675                | 12.8 (128)        | 0.8 (8)                     | 11.5 (115)                                               |
| 9–11 yr                 | 734                | 13.1 (131)        | 0.8 (8)                     | 11.9 (119)                                               |
| 12–14 yr                | 621                | 13.3 (133)        | 1.0 (10)                    | 11.7 (117)                                               |
| 15–19 yr                | 950                | 13.2 (132)        | 1.0 (10)                    | 11.5 (115)                                               |

Hb, hemoglobin; yr, year.

*Based on NHANES III data, United States, 1988–94.

*Menstrual losses contribute to lower mean and 5th percentile Hb values for group.
concentration rather than hematocrit. The latter measurement is a relatively unstable analyte and its measurement lacks standardization and is instrumentation dependent, since it is derived indirectly by automated analyzers.\textsuperscript{3,9} There is no evidence to support any different recommendation for the initial evaluation of anemia for children compared to adults.

In addition to Hb concentration, other reported results of the CBC may convey significant clinical information. The anemia of CKD is hypoproliferative, and in general, normochromic and normocytic. In this regard it is morphologically indistinguishable from the anemia of chronic disease.\textsuperscript{10} Folate or vitamin B\textsubscript{12} deficiencies may lead to macrocytosis, whereas iron deficiency or inherited disorders of Hb formation (e.g., \(\alpha\)- or \(\beta\)-thalassemia) may produce microcytosis. Iron deficiency, especially if long-standing, is associated with hypochromia (low mean corpuscular hemoglobin [MCH]). Macrocytosis with leukopenia or thrombocytopenia suggests a generalized disorder of hematopoiesis caused by toxins (e.g., alcohol), nutritional deficit (vitamin B\textsubscript{12} or folate deficiency), or myelodysplasia. When these findings are present, further diagnostic evaluation may be indicated.

The low erythropoietic activity that characterizes the anemia of CKD is consistent with insufficient erythropoietin stimulation. 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.\textsuperscript{1,11,12} Effective erythropoietic proliferative activity is most simply assessed by determination of the absolute reticulocyte count. Abnormalities of the white blood cell count and differential or platelet count are not typical of the anemia of CKD and should prompt investigation for other processes.

Reticulocyte count, which may be obtained with automated CBC testing, may be high in patients who have active blood loss or hemolysis, and may be low in hypoproliferative erythropoiesis with anemia.

**Iron status**

There are two important and distinct aspects of the assessment of iron status testing: the presence or absence of storage iron and the availability of iron to support ongoing erythropoiesis. The serum ferritin is the most commonly used test for evaluation of storage iron, for which the ‘gold standard’ remains examination of a bone marrow aspiration stained for iron.\textsuperscript{13} The transferrin saturation (TSAT; serum iron \(\times\) 100 divided by total iron binding capacity) is the most commonly used measure of the availability of iron to support erythropoiesis. The serum ferritin is affected by inflammation and is an ‘acute phase reactant’\textsuperscript{15} and, thus, ferritin values have to be interpreted with caution in CKD patients, especially those on dialysis in whom subclinical inflammation may be present.\textsuperscript{14}

Serum ferritin values \(\leq 30\) ng/ml (\(\leq 30\) \(\mu\)g/l) indicate severe iron deficiency and are highly predictive of absent iron stores in bone marrow.\textsuperscript{15,16} Ferritin values > 30 ng/ml (> 30 \(\mu\)g/l), however, do not necessarily indicate the presence of normal or adequate bone marrow iron stores. Studies assessing ferritin levels above which all or nearly all patients with CKD have normal bone marrow iron stores have produced varied results but most CKD patients, including those who are on HD, will have normal bone marrow iron stores when their serum ferritin level is \(\geq 300\) ng/ml (\(\geq 300\) \(\mu\)g/l). Even at serum ferritin levels of 100 ng/ml (100 \(\mu\)g/l) most CKD patients have stainable bone marrow iron stores.\textsuperscript{16-21} As will be discussed in Chapter 2, the serum ferritin and TSAT values are often used together to assess iron status, diagnose iron deficiency, and predict an erythropoietic response to iron supplementation (Supplementary Table 1 online).

Other tests of iron status, such as percentage of hypochromic red blood cells and reticulocyte Hb content may be used instead of, or in addition to, TSAT and ferritin levels if available. Measurement of hepcidin levels has not been shown to be clinically useful or superior to more standard iron status tests in patients with CKD.\textsuperscript{22,23}

**Vitamin B\textsubscript{12} and folate**

Folate and vitamin B\textsubscript{12} deficiency are uncommon but important causes of treatable anemia, typically associated with macrocytic red blood cell (RBC) indices. Limited data indicate a prevalence of vitamin B\textsubscript{12} and folate deficiency in \(\leq 10\%\) of HD patients; the prevalence in CKD patients is not known. Nonetheless, since these deficiencies are easily correctable, and in the case of vitamin B\textsubscript{12} may indicate other underlying disease processes, assessment of folate and vitamin B\textsubscript{12} levels are generally considered standard components of anemia evaluation, especially in the presence of macrocytosis. Folate deficiency is best detected in most patients with serum folate level testing; RBC folate levels can be measured when serum folate levels are equivocal or when there is concern that recent dietary intake may obscure underlying folate deficiency using serum levels alone.\textsuperscript{24}

**Additional tests**

Other tests, in addition to those indicated above, may be appropriate in individual patients and in certain specific clinical settings. For instance measurement of high sensitivity C-reactive protein (CRP) may be indicated if occult inflammation is a concern. In certain countries and/or in patients of specific nationalities or ethnicities, testing for hemoglobinopathies, parasites, and other conditions may be appropriate.

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SUPPLEMENTARY MATERIAL
Supplemental Table 1: Association between iron status and level of anemia in multivariable analyses. Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/anemia.php