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General Overview of Anemia in children with chronic kidney disease

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Abstract

Background: Some studies also cite the World Health Organization definition of anemia where children aged 6 months to 6 years are anemic if the hemoglobin count is less than 110 g/L and children aged 6–14 years are considered anemic if it is less than 120 g/L. The new NKF-KDOQI clinical practice guidelines use NHANES-III reference data to cite normative values in children.Anemia is a universal problem among children with chronic kidney disease (CKD). Lower levels of glomerular filtration rate (GFR) are associated with lower levels of hemoglobin, and in adults the latter is most pronounced when the GFR falls below 60 mL/min per 1.73 m2 .In children, the relationship between GFR and anemia is less clear.Most children with CKD will ultimately require treatment with Recombinant human erythropoietin, which may be administrated intravenously or subcutaneously, effectively treats anemia both in children with predialysis CKD and those on maintenance dialysis.

Keywords: Chronic Kidney Disease, Anemia, Children

Background

According to the classical definition of anemia in Nelson's *Textbook of Pediatrics*, 'anemia is defined as a reduction of the red blood cell volume or hemoglobin below the range of values for healthy persons. However, a great deal of controversy surrounds the definition of normal values of hemoglobin in children with CKD. Normal values adopted for children with CKD are based on observations of values in healthy children, the ranges of which are 120 g/L (range: 95–145 g/L) in 3-month-old children, 120 g/L (range: 105–140 g/L) in 6-month-old to 6-year-old children and 130 g/L (range: 110–160 g/L) in children aged 7–12 years **(1).**

Some studies also cite the World Health Organization definition of anemia where children aged 6 months to 6 years are anemic if the hemoglobin count is less than 110 g/L and children aged 6–14 years are considered anemic if it is less than 120 g/L. The new

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NKF-KDOQI clinical practice guidelines use NHANES-III reference data to cite normative values in children **(2).**

Earlier NKF-KDOQI guidelines suggested threshold values for hematocrit as well as hemoglobin to guide the initiation of work-up for anemia. However, a patient's hematocrit is highly vulnerable to volume status, hyperglycemia and the timing of sampling and, therefore, it has become a less useful measure of anemia. It is also affected by the technological approach used at different laboratories **(3).**

Epidemiology

Anemia is a universal problem among children with chronic kidney disease (CKD). Lower levels of glomerular filtration rate (GFR) are associated with lower levels of hemoglobin, and in adults the latter is most pronounced when the GFR falls below 60 mL/min per 1.73 m^2 .In children, the relationship between GFR and anemia is less clear. However, treatment of anemia in both adults and children has improved dramatically with the advent of regular erythropoietin (EPO) and iron therapy, and it has become possible to avoid routine transfusions to maintain a patient's hemoglobin. As well, the many studies performed in adults and relatively fewer studies carried out in children have demonstrated that improved hemoglobin levels are associated with benefits in quality of life, cognitive function, exercise capacity and cardiovascular function **(3).**

Mechanisms of Anemia in CKD

Anemia was first linked to CKD over 170 years ago by Richard Bright. As kidney disease progresses, anemia increases in prevalence, affecting nearly all patients with stage 5 CKD. Anemia in CKD is associated with reduced quality of life and increased cardiovascular disease, hospitalizations, cognitive impairment, and mortality. **(4).**

Anemia of CKD is a multifactorial process due to relative EPO deficiency, uremic-induced inhibitors of erythropoiesis, shortened erythrocyte survival, and disordered iron homeostasis. Recent work has identified hepcidin excess as a main contributor to the disordered iron homeostasis and anemia of CKD by impairing dietary iron absorption and iron mobilization from body stores. Improving our understanding of the molecular mechanisms underlying anemia of CKD holds promise for developing new pharmacologic agents that more closely target the underlying pathogenic mechanisms of this disease for improved efficacy and reduced treatment-related adverse outcomes. **(5).**

Lack of erythropoietin

Anemia in CKD is typically normocytic, normochromic, and hypoproliferative. The demonstration of a circulating factor responsible for stimulating erythropoiesis, and the

kidney as the main source of erythropoietin (EPO) in the 1950s engendered the hypothesis that EPO deficiency is the major cause of anemia in patients with CKD. Purification and cloning of EPO in the late 1970s and 1980s (enabled the development of immunologic assays for quantitating levels of circulating EPO. Although generally normal or slightly increased in anemia of CKD, EPO levels are considered inappropriately low relative to the degree of anemia, because similarly anemic patients with normal kidney function have 10–100 times higher EPO levels. One important limitation of such assays is that they measure all immunogenic EPO fragments, which do not all correlate with biologic activity. **(6)**

A reduced GFR may cause decreased sodium re-absorption in the tubules and because sodium re-absorption is the main determinant of energy consumption in the nephron, this may lead to a relative excess of oxygen, signaling a decrease in EPO production. The protein portion of EPO binds to an erythroid progenitor cell surface receptor to regulate bone marrow erythroid cell proliferation, differentiation and survival **(7).**

- ***Iron deficiency***

There is an 'absolute' and 'functional' iron deficiency that can be corrected with aggressive iron replacement therapy in CKD. Absolute iron deficiency occurs when iron stores are depleted as a result of loss or decreased intake; however, functional deficiency occurs when there is a need for a greater amount of iron to support hemoglobin synthesis than can be released from iron stores **(8).**

Inflammation and hepcidin

The presence of inflammation contributes to anemia as inflammatory mediators such as interleukin-6, interleukin-1 and tumor necrosis factor-α interfere with the maturation of red cell precursors in patients with CKD **(7).**

The anemia of inflammation has long been associated with elevated cytokine levels but for many years the underlying mechanism of this anemia was not known. The antimicrobial and iron regulatory peptide hepcidin has emerged as the link between the inflammatory response and the handling of iron for erythropoiesis.

Inflammatory cytokines directly induce hepcidin transcription,presumably as a mechanism to sequester iron from invading pathogens, leading to the iron sequestration, hypoferremia, and anemia that are hallmarks of many chronic diseases including CKD **(9).**

Bone Marrow Suppression

a) Inadequate dialysis:

In adults who are receiving dialysis, there is evidence that anemia is associated with inadequate dialysis. An increase in the dialysis dose leads to an improvement in Hb **(10).**

In a study of teenagers receiving HD, the children with Hb (Hemoglobin) levels of less than 11 g/dl had a slightly lower (urea clearance index). However, dialysis adequacy did not predict anemia in the multiple regression analysis, perhaps as a result of the high overall Kt/Vurea level in this patient population **(10).**

b) After Renal transplantation:

Hyperparathyroidism:

Whether excessive parathyroid activity per se causes anemia and resistance to erythropoietin (EPO) remains controversial. The potential mechanisms include a direct effect of parathormon (PTH) on endogenous EPO synthesis, on bone marrow erythroid progenitors, and on red blood cell survival (accelerated hemolysis). An indirect effect through the induction of bone marrow fibrosis **(12).**

Nutritional deficiencies

It is difficult to determine whether vitamin deficiencies play a significant role in causing anemia in chronic kidney disease. Most patients with chronic kidney disease take a multivitamin daily, although there is no strong evidence that this is beneficial. Therefore, even the prevalence of vitamin deficiencies in chronic kidney disease has been hard to establish **(13).**

CLINICAL CONSEQUENCES

The impact of anemia on patients with CKD is profound. In addition to the well-known symptoms of fatigue, dizziness, and shortness of breath, anemia has been associated with more severe adverse outcomes, such as cardiovascular complications including left ventricular hypertrophy and congestive heart failure **(14)**

Anemia is associated with several symptoms that lead to reduced quality of life, such as fatigue, dyspnea, insomnia, and headache. It is also related to reduced cognitive capacity. However, these symptoms are nonspecific and could be, in patients with CKD, a consequence of uremia. Since symptoms develop gradually, many patients do not report complaints spontaneously; however, when actively questioned, they may report limitations in their usual activities **(15).**

In addition, anemia is associated with left ventricular hypertrophy (LVH), an increased number of hospitalizations, a possible progression of CKD, and death. The increase in mortality occurs mainly when Hb≤ 8 g/dL **(16).**

Investigations for anemia

The diagnosis of anemia and the determination of etiology should be made using a systematic approach utilizing both clinical and laboratory investigations. A detailed history and physical examination including a family history, is invaluable for all patients. In terms of laboratory investigations, the NKF-DOQI guidelines recommend the

following tests: complete blood count, including serum hemoglobin, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, white blood cell count, differential count and platelet count **(17).**

Red blood cell indices on peripheral blood smears, especially mean corpuscular volume, can be useful in determining the etiology of anemia. Hypochromic microcytic erthryocytes with pencil cells is the classic presentation of iron deficiency anemia on a blood smear. However, CKD patients may have a normochromic and normocytic anemia **(18)**

NKF-KDOQI guidelines also recommend that reticulocyte counts should be obtained to measure the bone marrow response to anemia **(19).**

Management of anemia

Prevention

Anemia can develop during any stage of CKD in children and remains widely prevalent among the pediatric CKD population **(20).**

Therefore, the key to managing CKD in children may be to prevent anemia and to improve anemia management during all stages of CKD. Primary prevention measures for the development of anemia in children presenting with early stages of CKD need to be developed by means of systematic research. The current NKF-KDOQI guidelines recommend that hemoglobin be measured annually – at a very minimum – to screen for anemia **(19).** In both dialysis and non-dialysis CKD patients, judicious use of blood tests and the early institution of therapy is important to prevent the progression and prolongation of anemia.

Erythropoietin

Most children with CKD will ultimately require treatment with Recombinant human erythropiotin, which may be administrated intravenously or subcutaneously, effectively treats anemia both in children with predialysis CKD and those on maintenance dialysis **(21).** This part will be discussed in chapter (3).

Darbepoetin

Darbepoetin alfa, an erythropoietin analogue with a longer half-life than rHuEPO, is now widely used in children with CKD. The benefit of longer dosing intervals compared with those required for rHuEPO has made subcutaneous darbepoetin alfa an attractive alternative for treating anemia in young children and is likely to improve adherence. Darbepoetin alfa may be administered intravenously or subcutaneously, and while drug clearance, half-life and bioavailability are similar for adults and children regardless of route of administration, the absorption of the drug when given subcutaneously may be more rapid in children than in adults **(21).**

Iron

Iron repletion and maintenance is the second pillar of anemia management in kidney disease. Iron-deficient patients are also known to require higher doses of EPO to maintain target hemoglobin levels. The current NKF-KDOQI recommendation for targets of iron therapy is to maintain serum ferritin at >100 ng/mL and TSAT at >20% in pediatric HD, PD and non-dialysis CKD patients. It is important to use these targets conscientiously and to be aware of 'functional' iron deficiency. **(22).**

Oral iron supplements, though cheap, are often insufficient to maintain iron stores, especially in HD patients, due to excessive blood loss, poor absorption, poor compliance with medications and gastrointestinal side effects. In addition, timing of the oral iron dose may be difficult, as it needs to be separated from phosphate binders and antacids **(23).**

HD patients have many opportunities to experience iron loss, including excessive blood sampling, loss of blood through the dialyzer and tubing. IV doses of iron can be easily given to CKD patients who are on HD through the central venous access. Maintenance therapy aims to provide 1–2 mg/kg of elemental iron per week to achieve a TSAT between 20 and 50% and serum ferritin levels of 100–800 ng/mL. Higher doses of intermittent IV iron are usually given less frequently to non-dialysis CKD patients or PD patients. The risks of short-term and long-term toxicities of higher doses of IV iron need to be studied **(24).**

Adjunctive treatments for anemia

L-Carnitine Adjunctive treatment for anemia with L-carnitine is not routinely recommended. Only a very few small trials in children have examined the role of carnitine in improving anemia or effecting a change in the dose of EPO **(25).**

Vitamin C The role of supplemental vitamin C has been examined in adult HD patients with anemia, iron overload and elevated serum ferritin, and some studies have shown reduction in hyporesponsiveness to EPO or functional iron deficiency **(26).**

However, the long-term safety of administering IV vitamin C to HD patients is still undefined, with secondary oxalosis being the primary concern. The revised NKF-KDOQI guidelines do not recommend the use of vitamin C in children **(27).**

Folate The role of folate deficiency on chronic HD was examined in 15 subjects aged 8–20 years. In a 12-month crossover study where patients received no folate for 6 months and then 5 mg of folate for the next 6 months, the researchers found that after folate use mean hemoglobin increased by 11.4%. There is no specific recommendation regarding the routine use of folate in treatment of anemia in the new NKF-KDOQI guidelines for children **(28).**

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