Anemia of Chronic Kidney Disease

❖Anemia of Chronic Kidney Disease (CKD)

Anemia is a chronic, debilitating disease seen globally, but is especially common and severe in patients with CKD (peritubular cells being the source of erythropoietin, EPO). Before the introduction of the first erythropoiesis-stimulating agent (ESA), recombinant human erythropoietin (rHuEPO), anemic CKD patients were managed with blood transfusions and anabolic steroids. Even though rHuEPO revolutionized the management of anemia in patients with renal disease, limitations including efficacy, duration, route of administration, concomitant iron deficiency, & inflammation, have inspired advances in the treatment of anemia of CKD, as will be later discussed in this learning issue.

❖Erythropoietin Deficiency

At what stage of kidney insufficiency does low erythropoietin cause anemia?

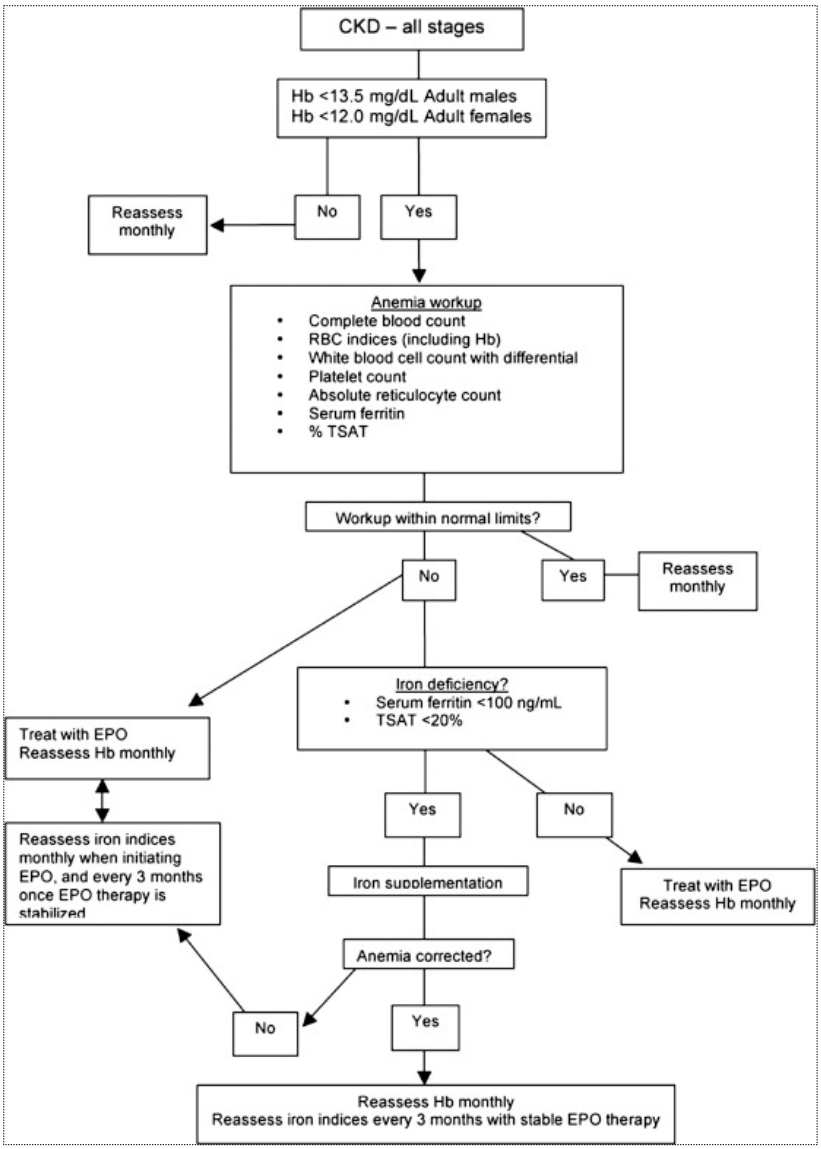
Anemia may result from both the loss of EPO synthesis in the kidney as well as the presence of erythropoiesis inhibitors. The severity of anemia in CKD is related to the duration and extent of kidney failure with the lowest Hb levels observed in anephric patients and those who commence dialysis at very severely decreased levels of kidney function.

In patients without CKD, EPO and Hb levels are negatively correlated, a feedback regulation that tends to be reversed in CKD patients[10-12]. In ESRD patients, feedback regulation is blunted. EPO levels in CKD patients remain in normal range compared with healthy controls, however, they experience lower than expected EPO levels for their degree of anemia.

Mercadal *et al*[13], investigated the timing of EPO deficiency and its determinants according to renal function in 336 CKD patients. In those with anemia, they also quantified the endogenous EPO response to Hb decreases, according to GFR level (mGFR). In patients with anemia, as defined by WHO (Hb <13 in men, <12 in women), EPO response to Hb level varied by mGFR. EPO and Hb levels were negatively correlated when mGFR <30. Overall, their study concluded that anemia in CKD is marked by an early relative EPO deficiency, however, several factors besides Hb may persistently stimulate EPO synthesis. Although EPO deficiency is likely the main determinant of anemia in patients with advanced CKD, the presence of anemia in those with mGFR >30 ml/min per 1.73m^2 calls for other explanatory factors.

❖Clinical Outcomes

Anemia is associated with worse outcomes in CKD patients. However, it remains to be determined whether the presence of anemia in CKD directly worsens prognosis or whether is simply a marker for the severity of other illnesses. Available evidence (large database analysis & population studies)[14] clearly show that low Hb levels are associated with higher rates of hospitalizations, cardiovascular disease, cognitive impairment, and other adverse patient outcomes, including mortality.



Clinical Evaluation of Anemia in CKD[15]

❖Epo Gene Therapy

Osada *et al* [1], reported on the results of gene therapy with human erythropoietin gene as a method of treating **anemia of renal origin**. They studied mice with polycystic kidney disease, transfected cells with a vector + human EPO gene, and inserted these cells intraperitoneally. They observed a significant increase in serum EPO levels and reticulocyte respose. This mode of therapy is very promising albeit some potential drawbacks (ie, irreversibility, overexpression, oncogenic potential) that must be worked out.

❖Erythropoietin-Mimetic Peptides

Erythropoietin-mimetic peptides are a family of peptides that have the same functional and biologic properties of Epo, but a completely different amino-acid structure. **Hematide** is a highly potent synthetic PEGylated peptide that binds to and activates the EPO receptor. It has demonstrated both *in vitro* activity (binding to EPO receptor, cell proliferation and differentiation, & intracellular signaling) and *in vivo* activity in multiple species (stimulation of erythropoiesis). Hematide does not share similar sequence homology with native Epo, thus antibodies that have developed in humans do not crossreact with Hematide, extending its clinical usefulness. Furthermore, clinical studies have observed a statistically and clinically significant increase in Hb response from baseline with an average maximum increase of 1.36 g/dl (+/- 0.39) (measured at 10-14 days post-dose, 0.1 mg/kg)[2]. This increase in Hb was sustained for >1 month. Overall, there was an increase in RBC count and hematocrit, transient decreases in ferritin, reticulocyte hemoglobin content, & endogenous Epo - all consistent with stimulation of erythropoiesis.

Hematide has also been specifically studied in patients with CKD. Single IV injections (0.05 mg/kg) of hematide were tolerated in patients with CKD[3]. The Hb increase in CKD patients seen at dose 0.05 mg/kg were similar to 0.1 mg/kg in normal, healthy volunteers. Similarly, the response was sustained for at least a month after a single injection.

❖Hypoxia-Inducible Factor (HIF) Stabilizers

Hypoxia-inducible factor (HIF) is a key regulator of erythropoietic gene expression. Additionally, HIF also regulates iron absorption, energy metabolism, pH, & angiogenesis. In the presence of oxygen, HIF is hydroxylated by an enzyme family of prolyl hydroxylases (PHs) which makes HIF more susceptible to degradation. **HIF PH inhibitors** inhibit PH, and therefore degradation, leaving higher concentrations of HIF available longer.

PH inhibitors induce complete erythropoiesis by coordinately regulating induction of Epo and improving bioavailability and utilization of iron. FG-2216 (first-generation PH I), elevates endogenous Epo and Hb in healthy subjects *and patients with CKD*[4-6]. Hb increases

were observed at a level of circulating endogenous Epo levels 1 and 2 orders of magnitude lower than those reported with rHuEPO-treated patients. This may be due to the other, synergistic effects of HIF stabilization, including iron mobilization.

❖New Approaches to Adjuvant Iron Therapy

In order to achieve a given target Hb, a balance of ESA and iron is necessary. CKD patients typically have absolute or functional iron deficiency and correcting this abnormality is challenging, as oral iron is generally ineffective, *particulary in patients on hemodialysis.* Furthermore, CKD patients are unable to mobilize iron from stores normally.

Ferumoxytol[7-8] is a polysaccharide-coated iron oxide under development with reported advantages of being non-allergenic and well tolerated in rapidly administered, large doses. **Iron oligosaccharide** is another agent being investigated for iron therapy. It is thought to have lower incidence of hypotensive events at higher doses. **Ferric pyrophosphate**[9] is a water soluble form of iron the can be delivered via dialysate in ESRD patients.

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