
بسم الله

Management of Anemia in CKD Patients

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1.ESAs.

Drugs may be erythropoietin analogs or may stimulate erythropoiesis in other ways. There are many different erythropoietin analogs : Epoetin alfa (Epogen, Procrit) and darbepoetin alfa (Aranesp).

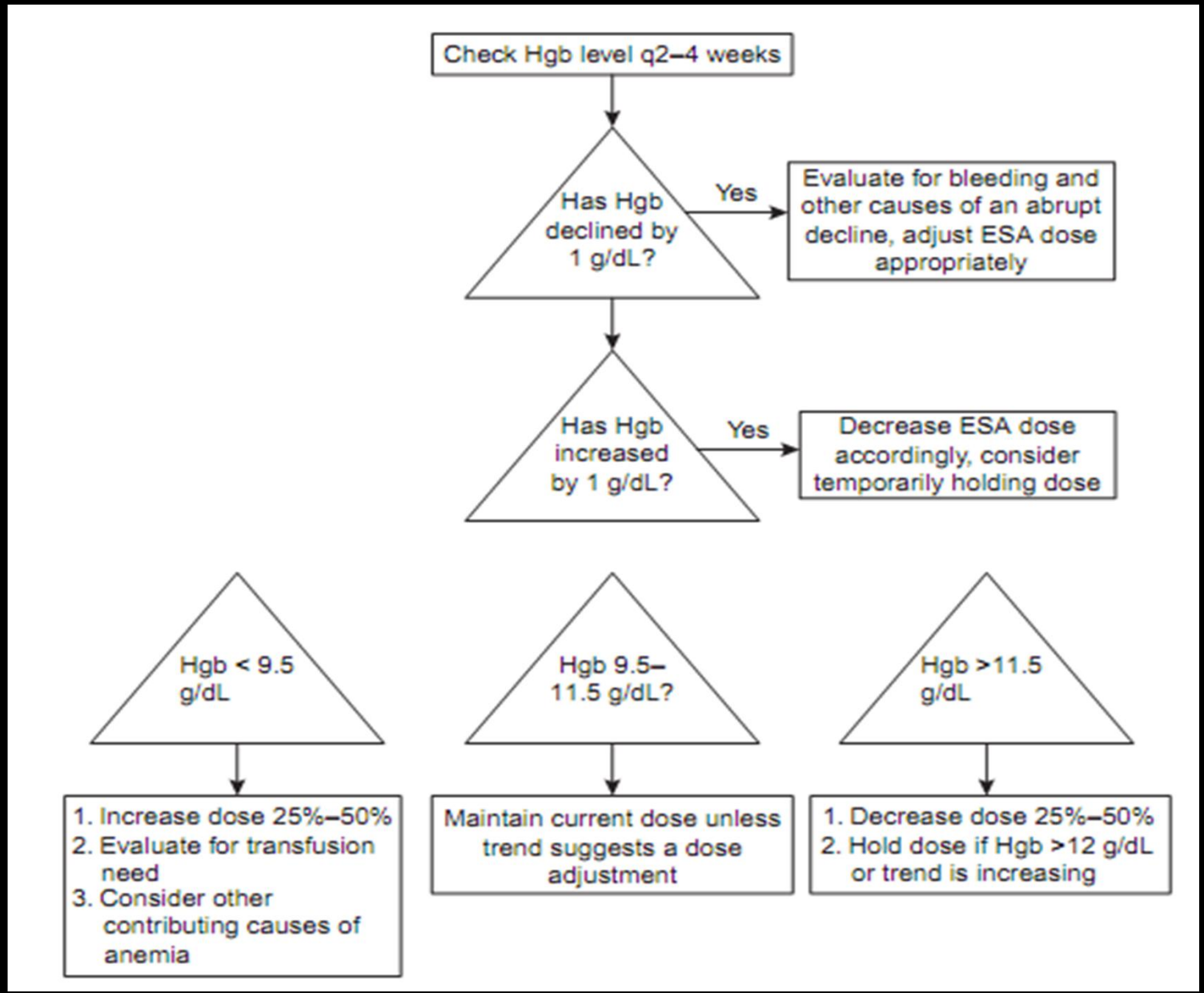
- **Epoetin alfa** is a glycoprotein that is indistinguishable from native erythropoietin. It is manufactured by recombinant DNA technology and has a molecular weight of 30,400 Da and a circulating half-life after intravenous administration of approximately 8 hours.

- **Darbepoetin alfa** is a synthetic analog of erythropoietin with increased carbohydrate content that increases the molecular weight by approximately 20% compared with native erythro- poietin. As a result of the altered structure, the drug's phar- macokinetics are changed and the serum half-life is increased to approximately three times longer, 24 hours, compared with epoetin alfa.

- One new class of ESAs currently under development acts to stabilize hypoxia inducible factor-1 (HIF). Synthesis of HIF is increased in the presence of hypoxia, and HIF acts to increase the transcription of EPO. HIF is rapidly de- graded when normoxic conditions are present, and drugs that stabilize HIF result in increased endogenous erythropoietin production, even in anephric individuals.

Indications for ESA therapy and target hemoglobin.

ESA therapy should generally be initiated in CKD patients when the Hgb falls below 10 g/dL.
(KDIGO) anemia guidelines (2012) simply recommend that Hgb for dialysis patients should not exceed >11.5 g/dL .
A reasonable hemoglobin target for patients on dialysis would be 9.5–11.5 g/dL .


Check Hgb level q2–4 weeks
Has Hgb declined by 1 g/dL?
Yes
Evaluate for bleeding and other causes of an abrupt decline, adjust ESA dose appropriately
Has Hgb increased by 1 g/dL?
Yes
Decrease ESA dose accordingly, consider temporarily holding dose
Hgb < 9.5 g/dL
1. Increase dose 25%–50%
2. Evaluate for transfusion need
3. Consider other contributing causes of anemia
Hgb 9.5–11.5 g/dL?
Maintain current dose unless trend suggests a dose adjustment
Hgb >11.5 g/dL
1. Decrease dose 25%–50%
2. Hold dose if Hgb >12 g/dL or trend is increasing

2.Intravenous iron.

Four preparations are available in the United States: Iron dextran, ferric gluconate, ferumoxytol, and iron sucrose.

3.Red blood cell transfusions.

Red blood cell (RBC) transfusions will immediately raise hemoglobin (Hb) levels. However, they may be associated with significant complications that include transfusion-transmitted infection (very rare), immunologic sensitization, iron overload syndromes, volume overload, and/or transfusion reactions. Transfusions are rarely administered in chronic dialysis facilities but are indicated for treatment of severe or symptomatic chronic anemia unresponsive to erythropoiesis-stimulating agent (ESA) and iron therapy.

4.Ascorbic acid.

Although the literature is mixed, several studies have found that intravenous ascorbic acid may improve epoetin responsiveness for patients on hemodialysis. A typical regimen is intravenous vitamin C given three times weekly with the hemodialysis treatment. Deved (2009) conducted

Since vitamin C may lead to increases in oxalate production, appropriate caution must be used in patient selection and duration of therapy.

5.Folic acid and vitamin B12

Folate deficiency is typically treated with oral folic acid (1 to 5 mg daily, more than 1mg in hemodialysis patients who need more folate for DNA synthesis.)
Treatment for vitamin B12 deficiency is necessary in hemodialysis patients. (0.006 mg/day.)
Higher doses may be appropriate for some patients who are severely malnourished.

Management of Anemia in Non-dialysis CKD patients

Anemia is common among nondialysis CKD patients, and the prevalence increases as the glomerular filtration rate (GFR) declines.

As an example, based upon over 15,000 participants in the National Health and Nutrition Examination Survey (NHANES), the prevalence of anemia (hemoglobin [Hb] <12 g/dL in men and <11 g/dL in women) increased from 1 percent among patients with an estimated GFR (eGFR) of 60 mL/min/1.73 m^2 to 9 percent at an eGFR of 30 mL/min/1.73 m^2 and to 33 to 67 percent at an eGFR of 15 mL/min/1.73 m^2

The initial evaluation of anemia is generally the same for CKD patients as in the general population. The evaluation should include CBC, red blood cell (RBC) indices, reticulocyte count, serum iron, total iron-binding capacity (TIBC), percent transferrin saturation (TSAT), serum ferritin, serum folate and vitamin B12 levels, and testing for occult blood in stool.

Among some CKD patients, the treatment of anemia includes ESAs and/or iron.

INDICATIONS FOR TREATMENT WITH IRON

- We recommend giving iron to most CKD patients who have a TSAT ≤20 percent and a serum ferritin concentration ≤100 ng/mL. Such patients are likely to have decreased iron stores (ie, absolute iron deficiency).
- We give iron to most **anemic** CKD patients who have a TSAT ≤30 percent and ferritin ≤500 ng/mL. Anemia is defined as an Hb concentration <13.0 g/dL for adult males and postmenopausal women and an Hb <12.0 g/dL for premenopausal women.
- Although most CKD patients with TSAT of 20 to 30 percent and ferritin 100 to 500 ng/mL will have normal iron stores on bone marrow biopsy, many will respond to iron with an increase in Hb or decrease in erythropoiesis-stimulating agent (ESA) dose.
- We do not treat with iron patients who have a TSAT >30 percent, since such patients are unlikely to respond to iron.
- We do not routinely administer iron to patients with ferritin levels >500 ng/mL.

ROUTE OF ADMINISTRATION

Iron may be given orally or intravenously. The route of administration is selected based upon the severity of anemia and iron deficiency, the patient's ability to tolerate oral iron, the response to prior oral iron therapy, history of adverse reactions to intravenous iron, and the availability of venous access.

We give oral iron to most nondialysis CKD patients who are selected for iron therapy.

Oral iron is inexpensive, readily available, and does not require intravenous access.

We give ***intravenous iron*** to selected patients who require more rapid repletion of iron or are unlikely to be effectively treated with oral iron, including most patients with symptomatic anemia, providing blood transfusion can be safely deferred.

We give intravenous iron to patients with:

- Severe iron deficiency (ie, transferrin saturation [TSAT] <12 percent)
- Severe anemia (hemoglobin [Hb] <7 g/dL) in asymptomatic patients
- Risk of ongoing blood loss (such as a patient with chronic gastrointestinal blood loss)
- History of side effects to oral iron
- History of not responding to oral iron in the past

ADVERSE EFFECTS

Intravenous iron may be associated with an increased risk of adverse effects in nondialysis CKD patients, although data are conflicting.
In a few randomized trials compared to oral iron, intravenous iron had more infection and cardiovascular events.

Yet in a meta-analysis of 16 trials and 2612 patients (including 10 trials of 2129 nondialysis CKD patients), there was no difference between oral and intravenous iron-treated patients in all-cause mortality and adverse effects.

KDIGO guidelines have recommended that either oral iron therapy or intravenous iron therapy can be given in nondialysis patients.

GOALS OF THERAPY

The goal of iron therapy is to correct absolute iron deficiency and/or to increase Hb level to that desired for the particular patient.

We generally provide sufficient iron to accomplish this while attempting to maintain the TSAT ≤30 percent and the ferritin level ≤500 mg/mL. Although the dose varies among individual agents, a course of intravenous iron usually provides 1000 mg elemental iron.

Some patients will not increase Hb to desired values despite achieving a TSAT of approximately 30 percent. Such patients may be candidates for treatment with ESAs.

Iron indices should be re-evaluated after therapy, typically one month following a dose of intravenous iron or the last dose of a planned series of infusions, and every three months among patients receiving oral iron. For patients treated with oral iron, we usually switch to intravenous treatment if iron status tests and Hb are not improving and remain below goal.

Iron indices generally respond to intravenous iron therapy. Patients who do not achieve target TSAT and ferritin values, or at least show significant improvement in iron stores, despite intravenous iron should be evaluated for sources of blood loss, particularly gastrointestinal bleeding.

ORAL IRON

We usually give ***ferrous sulfate*** 325 mg three times daily. Ferrous sulfate provides 65 mg elemental iron per 325 mg tablet. Ferrous sulfate should be given between meals, if tolerated. Intestinal iron absorption may be normal or impaired in patients with renal failure and may be reduced by food and antacids. Giving one of the doses at bedtime may be a simple and effective expedient.

Multiple other agents are available but tend to be more expensive, without greater efficacy or consistently fewer side effects. As examples:

- **Ferric citrate** is an oral phosphate binder that may be useful for oral iron supplementation. Ferric citrate has been shown in both dialysis and nondialysis CKD patients to increase TSAT and serum ferritin concentration and to reduce the use of intravenous iron and ESAs.

- **Heme iron polypeptide** was initially described to have better absorption and bioavailability than other oral iron products.

- **Liposomal** preparations may have greater absorption from the gastrointestinal tract and be better tolerated than ferrous sulfate, although more comparative data are required.

INTRAVENOUS IRON

Iron dextran is associated with a higher incidence of serious adverse effects, particularly anaphylaxis, than iron sucrose and ferric gluconate in sucrose complex.

- **Ferumoxytol:** The preferred dose is 510 mg dose, followed by a second 510 mg injection three to eight days after the first dose, though some prescribe a single 1020 mg dose. Two doses are usually sufficient to replete iron to therapeutic targets.

- **Iron sucrose:** The preferred dose is 200 mg x five doses administered over two weeks. This dose is generally well tolerated.

- **Ferric gluconate in sucrose complex**: The preferred dose is 250 mg once weekly for three to four doses, as needed.

- **Ferric carboxymaltose:** Two doses of 750 mg may be given in one week. Ferric carboxymaltose is effective and relatively safe.

- **Iron isomaltoside —** Iron isomaltoside is a high-dose intravenous preparation. Unlike most other intravenous iron preparations, iron isomaltoside may be given in single doses exceeding 1000 mg.

Side effects

The most common side effects are hypotension, nausea, vomiting, and abdominal discomfort; these effects are generally self-limited and do not require intervention other than perhaps slowing the rate of iron infusion. In addition, renal tubular injury has been reported in nondialysis patients who have received intravenous iron, although an effect on glomerular filtration rate (GFR) has not been demonstrated.

Management of Anemia in Hemodialysis patients

Dialysis patients are often iron deficient due to gastrointestinal bleeding, blood drawing, operations, and the dialysis treatment itself. Hemodialysis patients lose an average of 1 to 2 g of iron per year.

According to the (KDIGO) guidelines:

1. **Transferrin saturation (TSAT) ≤20 percent and ferritin ≤200 ng/mL, we give a loading dose of intravenous (IV) iron, providing an underlying infection has been excluded, regardless of the Hb and regardless of whether patients are treated with an ESA.**

Among patients who are not already on an ESA, the loading dose of iron should be repeated until the TSAT is >20 percent.
Iron should be given prior to the initiation of treatment with an ESA.
Patients who do not respond to the loading dose of iron should be evaluated for potential sources of bleeding, particularly gastrointestinal blood loss.

Among patients who are being treated with an ESA and have these laboratory values, IV iron should be administered while continuing ESA treatment (unless goal Hb has been reached or exceeded, in which case the ESA is stopped).

Among patients who are already on an ESA, the correction of iron deficiency, which may develop as the result of depletion of iron stores due to the ESA-induced increase in erythropoiesis, may allow for a lower ESA dose and decrease the risk of ESA resistance.

2. **Transferrin saturation (TSAT) ≤30 percent and ferritin ≤500 ng/mL and who have Hb <10 g/dL or are being treated with an ESA,**

we give a loading dose of iron, providing an underlying infection has been excluded. As above, among patients who are not being treated with an ESA, iron should be given prior to ESA treatment.

Among patients who treated with an ESA and have these laboratory values, IV iron should be administered while continuing ESA treatment (unless goal Hb has been reached or exceeded, in which case ESA is stopped).

Although most chronic kidney disease (CKD) and hemodialysis patients with TSAT of 20 to 30 percent and ferritin 200 to 500 ng/mL will have normal iron stores on bone marrow biopsy, many will respond to IV iron with an increase in Hb or decrease in ESA dose.

3. ESA-treated patients

For all hemodialysis patients who are being treated with an erythropoiesis-stimulating agent (ESA), we suggest maintenance or low-dose iron irrespective of the TSAT, providing the ferritin is ≤500 ng/mL. ESA therapy requires significant amounts of supplemental iron for effective erythropoiesis.

Approximately 1000 mg is required among hemodialysis patients to raise Hb levels from approximately 8 g/dL to 11 to 12 g/dL with the initiation of ESA therapy.

Among ESA-treated patients, after target Hb levels are achieved, approximately **250 to 500 mg of iron may be required every three months** to maintain adequate iron stores to support erythropoiesis with ESA therapy.

4. **Ferritin greater than 500 ng/mL**

We do not routinely administer IV iron to patients who have ferritin levels above 500 ng/mL, regardless of the TSAT and Hb, since no studies have proven a benefit of iron among such patients. However, each patient should be individually assessed, and some clinicians continue IV iron administration in patients with ferritin levels >500 ng/mL.

Management of Anemia in PD patients

Anemia is common among peritoneal dialysis patients. Anemia underlies many of the symptoms associated with reduced kidney function and is associated with increased mortality and hospitalizations.

Iron deficiency is a common reversible cause of anemia among peritoneal dialysis patients.

- Anemia is common among dialysis patients and underlies many of the symptoms associated with reduced kidney function. Screening for and treating anemia is a routine part of the care of peritoneal dialysis patients.

- All patients should be screened for anemia upon initiation of maintenance peritoneal dialysis, particularly if they have not been closely followed prior to initiation. Patients are screened with a complete blood count (CBC). Patients who are found to be anemic should be evaluated for cause.

- We continue to screen peritoneal dialysis patients for anemia and iron deficiency at least every three months. In addition, hemoglobin (Hb) should be checked whenever clinically indicated (such as after major surgical procedures, hospitalization, or bleeding).

- Among peritoneal dialysis patients who are treated with erythropoiesis-stimulating agents (ESAs), we measure Hb at least monthly. We measure Hb more frequently during the initiation and titration of ESA (ie, every two weeks).

- The goal of treatment is to mitigate any symptoms due to anemia and to reduce the likelihood of needing a blood transfusion. The selection of the individual therapy depends on the severity of anemia and on the presence of iron deficiency.

- **Among most peritoneal dialysis patients, the treatment of anemia includes ESAs and/or iron.**

- For peritoneal dialysis patients who are selected for ESA treatment, we suggest subcutaneous rather than intravenous (IV) ESA administration. Subcutaneous administration is associated with a lower required dose and a lower risk of death and/or hospitalization for cardiovascular events. A preferred initial dose is approximately 50 to 100 units/kg/week, with further titration based on Hb response.

- Hb targets for peritoneal dialysis patients are the same as those for hemodialysis patients. For most peritoneal dialysis patients who are treated with ESAs, we maintain Hb levels between 10 and 11.5 g/dL. We individualize therapy in some patients who may have improvements in quality of life at Hb ≥11.5 g/dL and will be prepared to accept the risks associated with higher Hb targets. We do not target Hb concentration >13 g/dL.

- The adverse effects of subcutaneous erythropoietin are generally similar to those for IV erythropoietin. Patients using subcutaneous injection may have pain at the site of injection.

INDICATIONS FOR IRON ADMINISTRATION IN PD PATIENTS

- We give intravenous (IV) iron to all peritoneal dialysis patients who have a TSAT ≤20 percent and a serum ferritin concentration ≤100 ng/mL, regardless of the Hb, providing an active infection is not present. Such patients likely have absolute iron deficiency.

- We give IV iron to peritoneal dialysis patients with moderate or severe anemia (defined as Hb <10 g/dL), TSAT ≤30 percent, and ferritin ≤500.

- The treatment of patients with mild anemia (Hb 10 to 12 g/dL) in the absence of absolute iron deficiency (defined as TSAT ≤20 percent and ferritin ≤100 ng/dL) is controversial. Some clinicians treat such patients with IV iron, providing TSAT is ≤30 and ferritin is ≤500 ng/dL. Others treat with oral iron if TSAT <25 percent and ferritin <300 ng/dL. Still others do not treat mild anemia unless there is clear evidence of absolute iron deficiency (ie, TSAT ≤20 percent and ferritin ≤100 ng/mL).

- We do not treat with iron patients who have a TSAT >30 percent, since such patients are unlikely to respond to iron. We do not routinely administer iron to patients with ferritin levels >500 ng/mL and anemia, although each patient should be individually assessed.

Thank you.

The End.