In the name of God

Anemia

The anemia of chronic kidney disease (CKD) is primarily due to insufficient production of the glycoprotein hormone erythropoietin (EPO). Although EPO can be produced in many of the body's tissues, EPO required for erythropoiesis generally is produced by endothelial cells in proximity to the renal tubules. As renal excretory function is lost, there is a relative decline in the production of EPO that correlates with the declining glomerular filtration rate. The severity of the resulting anemia varies, but if untreated, then hematocrit values in end-stage kidney disease (ESKD) of 18%–24% are typical.

Symptoms. The manifestations of anemia may be due both to the effects of decreased oxygen delivery to tissues and to the heart's compensatory changes. The most prominent symptoms of anemia are fatigue and dyspnea. Symptoms develop slowly, and the patient may gradually constrict his or her activities in compensation. The patient's overall sense of well-being is diminished. Other symptoms may include difficulty concentrating, dizziness, sleep disorders, cold intolerance, and headaches. The heart responds to diminished oxygen-carrying capacity of blood by attempting to maintain systemic oxygen delivery with increased cardiac output and left ventricular hypertrophy. Patients may notice worsening dyspnea and palpitations at this stage.

Other problems include deranged hemostatic function, impaired immune function, and diminished cognitive and sexual function. Exacerbations of angina, claudication, and transient ischemic attacks may also be observed.

Physical examination. The primary physical examination finding of anemia is pallor, which may be best detected on the palms of the hands, the nail beds, and the oral mucosa. Asystolic ejection murmur due to increased cardiac flow may be heard over the precordium

Epoetin alfa (Epogen,Procrit) and darbepoetin alfa (Aranesp) are currently available in the United States,and methoxy-polyethyleneglycol-epoetin beta (Mircera) is widely used in Europe and probably will be available shortly in the United States. Peginesatide (Omontys) currently is not being marketed in the United States, after a substantial number of allergic reactions occurred with its use.

Epoetin alfa is a glycoprotein that is indistinguishable from native erythropoietin. It is manufactured by recombinant DNA technology and has a molecular weight of 30,400Da 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 erythropoietin. As a result of the altered structure, the drug's pharmacokinetics are changed and the serum half-life is increased to approximately three times longer, 24 hours, compared with epoetin alfa. **Mircera** has an unusually long serum half-life of approximately 5.5 days.

Peginesatide is a synthetic peptide attached to polyethyleneglycol that mimics the structure of erythropoietin, but that has no amino acid sequence homology to EPO. Biological analogs of ESAs, so-called biosimilars, have been manufactured and are in use outside of the United States

One new class of ESAs currently under development acts to stabilize hypoxiainducible 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 degraded when normoxic conditions are present, and drugs that stabilize HIF result in increased endogenous erythropoietin production, even in anephric individuals. These drugs will be an important new class of ESAs if they are demonstrated to be safe and effecti Benefits of anemia treatment with ESA.

Effect on outcomes. Cross-sectional and retrospective studies have suggested that anemia in patients undergoing hemodialysis is associated with increased mortality, particularly when the hemoglobin concentration is <10 g/dL (100 g/L). Analyses of large administrative and clinical databases have shown that risk for mortality, hospitalization rate, and hospitalization days continue to decrease even at hemoglobin levels >11 g/dL (110 g/L). In contrast to these observational studies, interventional studies have not demonstrated improved outcomes following normalization of hemoglobin with ESA treatment. In fact, cardiovascular outcomes in these studies generally have been worse Reduction in transfusion-related complications.

Prior to ESA therapy, up to 20% of patients on dialysis required frequent transfusions with attendant risk of immediate transfusion reactions, viral infection, iron overload, and immune sensitization. The rate of blood transfusion has been greatly reduced by the use of ESA therapy **Improved quality of life and overall sense of well-being.** Various assessment tools have documented an improved quality of life and functional status in ESKD patients treated with ESA.

Patients feel less fatigued and their exercise capacity increases. Symptoms that had been disabling in the pre-ESA era are now easily managed. However, the target level of hemoglobin for optimized quality of life is not completely known. Whether higher hemoglobin targets further improve quality of life is unclear. Some studies suggest that improvements may continue as hemoglobin is raised toward the normal range, while others have found no improvement in quality of life despite higher hemoglobin targets

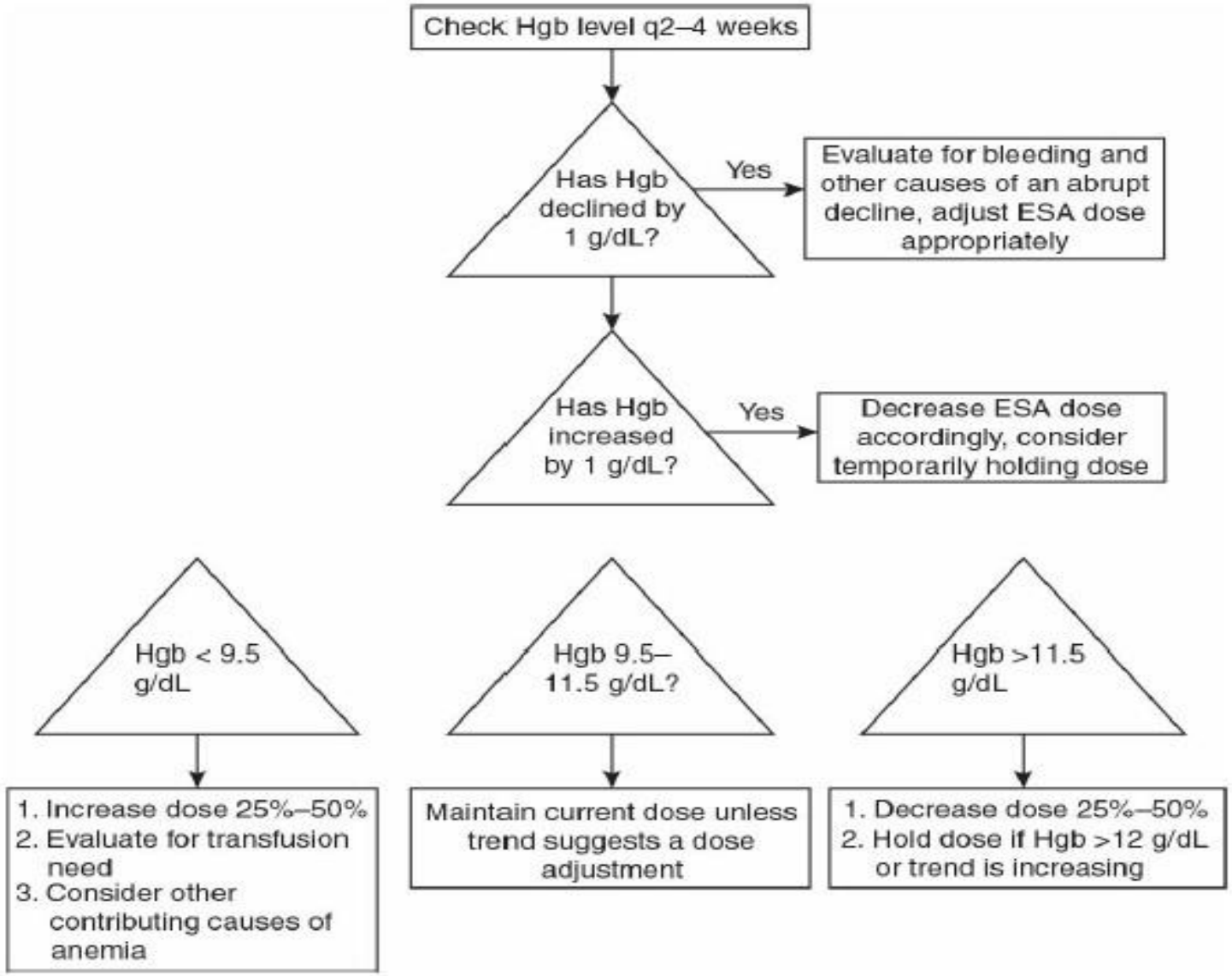
Indications for ESA therapy and target hemoglobin. ESA therapy should generally be initiated in CKD patients when the Hgb falls below 10 g/dL (100 g/L). The optimal Hgb level for a patient with ESKD is not known. The Kidney Disease: Improving Global Outcomes (KDIGO) anemia guidelines (2012) simply recommend that Hgb for dialysis patients should not exceed >11.5 g/dL (115 g/L). This recommendation is in some conflict with current FDA prescribing instructions, which recommend holding ESA dosing when the hemoglobin is >11.0 g/dL (110 g/L). A reasonable hemoglobin target for patients on

dialysis would be 9.5–11.5 Subcutaneous versus intravenous ESAs

. The subcutaneous route improves the efficiency of therapy, resulting in a reduced dosing requirement (of about 25%) for shortacting ESAs, specifically epoetin alfa. (Kaufman, 1998). When epoetin is given intravenously, its short half-life probably results in some drug never binding to erythropoietin receptors prior to clearance of epoetin from the circulation. When given subcutaneously, the serum half-life of epoetin is extended, allowing for more efficient receptor binding and a greater erythropoietic effect

Initial dose. Treatment with ESA should ideally be initiated, if required, in the pre-ESKD period. If treatment needs to be initiated for a patient already on dialysis, reasonable starting doses of epoetin alfa for a hemodialysis patient would be 2,000–3,000 units three times per week, and for a peritoneal dialysis patient 6,000 units once per week. A typical dose of darbepoetin alfa would be approximately 25 mcg once weekly for a hemodialysis patient or 60 mcg every 2 weeks for a patient on peritoneal dialysis. A typical dose of Mircera would be 150 mcg given once monthly. Selection of a specific dose requires clinical judgment as to how symptomatic the patient is and the starting level of hemoglobin.

Initial response and plateau effect. During the initiation phase of therapy, hemoglobin should be checked every 1–2 weeks, and the ESA dose adjusted as needed. It is very common during the initiation of treatment for a "plateauing" of effect to occur; either the hemoglobin stops increasing, or escalating doses of ESA are required to reach therapeutic targets. This period of blunted response is often due to the development of iron deficiency. Once the target level of hemoglobin has been reached, the hemoglobin should be checked every 2–4 weeks. During this maintenance phase of therapy, the dose of ESA should be adjusted on the basis of subsequent changes in hemoglobin (Fig. 34.1).



Flow chart for adjusting the ESA dose based on hemoglobin (Hgb) results for dialysis patients.

Side effects of ESA therapy

Worsening of hypertension. This is a common problem during the partial correction of anemia with ESA therapy. In some patients, there will be a need to increase antihypertensive medication doses. However, it is rare for ESA to be withdrawn because of uncontrollable hypertension. Risk factors include preexisting hypertension, a rapid increase in hemoglobin, the presence of dysfunctional native kidneys, and severe anemia prior to treatment. The cause of the hypertensive effect is incompletely understood

Factors that may contribute include the partial reversal of hypoxicvasodilation as the hemoglobin rises, reduced nitric oxide, increased cytosolic calcium levels, increased plasma endothelin levels, activation of the renin–angiotensin–aldosterone system and others. Various antihypertensives, including long-acting calcium channel blockers, are effective for treating hypertension associated with ESA.

Seizures. These may occur in a small number of patients during periods of rapidly increasing hemoglobin in association with hypertension. The risk of seizures is small using current ESA dosing protocols

Graft clotting. The increase in blood viscosity with higher hemoglobin values from either ESA therapy or other causes could theoretically cause increased dialyzer and arteriovenous graft clotting. Studies to date have not consistently demonstrated an increased risk of thrombosis when the hemoglobin is raised to the 11–12 g/dL (110–120 g/L) range. The impact of higher hemoglobin levels is controversial. It should be clear that some patients may experience substantial hemoconcentration during or after the hemodialysis treatment, and effects on blood viscosity and risk for access thrombosis may be a particular concern in this setting.

Stroke. The risk of stroke has been increased in some of the randomized trials of ESAs where a relatively high Hgb level has been targeted, but this was not noted in all such studies

Effect on *Kt/V.* During dialysis, urea is removed from both red cells and plasma, and so urea clearance and Kt/V-urea are not affected by an increase in the Hgb. Creatinine and phosphorus are removed from the plasma only during passage of blood through the dialyzer, and as the Hgb is increased, at any given blood flow rate, the plasma flow rate and creatinine and phosphorus clearances will be proportionately reduced.

Serum ferritin. Ferritin is a protein used to store iron inside cells in a nontoxic form. Free iron is toxic to cells because it can generate free radicals. Although most ferritin is intracellular, some appears in the circulation and reflects iron stores,although the function of ferritin is to store iron and not to transport it in the circulation. Because serum ferritin is cleared by the liver, in hepatic insufficiency,serum levels may be markedly increased. A more common cause of increased serum ferritin is any sort of inflammation, as ferritin is an acute phase reactant. Serum ferritin levels can also be high in certain cancers and with malnutrition. If the serum ferritin level is <200 mcg/L, the likelihood of iron deficiency is quite high. However, absolute iron deficiency can be present with much higher serum ferritin levels in the presence of inflammation.

Transferrin saturation. Transferrin is a glycoprotein that normally transports iron in the blood. In diagnosing anemia, transferrin levels are not measured directly.Instead, one can measure total iron binding capacity (TIBC) after a loading a serum sample with iron. This test measures how much iron the blood can carry in non-Hgb form, and is an indirect reflection of the transferrin level. Normal values for TIBC are 240–450 mcg/dL (43–81 mcmol/L). The percent transferrin saturation (TSAT) is calculated by dividing the serum iron by the TIBC, and the value for TSAT normally is about 30% with a range of 20%–50%.

intensification of iron therapy for hemodialysis patients should be considered at a serum ferritin of <200 ng/mL or TSAT of <20%. We would recommend maintaining TSAT >20% and serum ferritin > 100 ng/mL in peritoneal dialysis patients. Iron testing should usually be delayed for 1 week after treatment with intravenous iron.**Functional iron deficiency** can manifest as a low TSAT with normal or elevated ferritin levels.With inflammation and **reticuloendothelial blockade**, ferritin levels are typically increased, but TSAT may be normal, as serum iron may be low, but inflammation also lowers serum transferrin, and so the TSAT is often not reduced.

Iron treatment Oral iron. Oral iron preparations are safe and relatively inexpensive. However,these supplements are associated with poor efficacy and troublesome side effects, such as constipation, dyspepsia, bloating, or diarrhea. Three randomized trials have compared oral iron with either placebo or no iron treatment in hemodialysis patients; none of the three was able to demonstrate any efficacy for oral iron.therefore, oral iron should not be used for most hemodialysis patients. For patients on peritoneal dialysis, oral iron is much more convenient than intravenous iron. Since these patients experience less chronic blood loss, oral iron may be sufficient to maintain iron stores. Intravenous iron therapy should be used in peritoneal dialysis patients when resistance to ESA is present and the serum ferritin is <100 ng/mL and the TSAT is <20%.

Dosage and administration. Oral iron usually is given as ferrous sulfate, fumarate, or gluconate, in a dosage of 200 mg of elemental iron per day. The timing of the iron dose is important; ideally, iron should be taken on an empty stomach to optimize efficacy. The primary sites of iron absorption are the duodenum and proximal jejunum, and gastrointestinal symptoms are proportional to the amount of elemental iron presented to the duodenum at a single time; reduction of symptomatology may require changing the oral preparation, using pediatric dosages at more frequent intervals, or even taking the iron dosage with food.Others have suggested giving the medication during dialysis sessions (e.g., at the beginning and the end of the session) to help ensure patient compliance. Yet another strategy is to give oral iron only at bedtim

Intravenous iron. Four preparations are available in the United States: Iron dextran,ferric gluconate, ferumoxytol, and iron sucrose. Intravenous iron therapy has superior availability and efficacy when compared with oral iron therapy. In hemodialysis patients, the target hemoglobin level is difficult to achieve without intravenous iron treatment. As a result, most hemodialysis patients will require intravenous iron on a regular basis. In contrast, intravenous therapy costs more, and its safety profile is less clear than that of oral iron. There are two commonly used intravenous iron dosing strategies. One is to treat established iron deficiency with a repletive 1,000-mg dose administered over 8–10 consecutive hemodialysis treatments. Alternatively, since iron deficiency occurs so frequently in hemodialysis patients, a weekly maintenance dose of 25–100 mg may be used

Iron sucrose. Intravenous iron sucrose was approved for use in the United States in 2000 and has been in use in Europe for many years. Like sodium ferric gluconate, the other widely used nondextran form of iron, reports generally indicate a good safety and efficacy profile. No serious adverse reactions occurred in 665 hemodialysis patients receiving 8,583 doses of the drug (Aronoff, 2004). The drug may be administered as iron replacement therapy, 100 mg for 10 consecutive doses, or as a weekly dose of 25–100 mg

Thanks

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attention

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