ERYTHROPOIETIN

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**Structure & Function**

When an individual bleeds or becomes hypoxic, hemoglobin synthesis is enhanced, and production and release of red blood cells from the bone marrow **(erythropoiesis)** are increased (see Chapter 32). Conversely, when the red cell volume is increased above normal by transfusion, the erythropoietic activity of the bone marrow decreases. These adjustments are brought about by changes in the circulating level of **erythropoietin,** a circulating glycoprotein that contains 165 amino acid residues and four oligosaccharide chains that are necessary for its activity in vivo. Its blood level is markedly increased in anemia

Erythropoietin increases the number of erythropoietin-sensitive committed stem cells in the bone marrow that are converted to red blood cell precursors and subsequently to mature erythrocytes (see Chapter 32). The receptor for erythropoietin is a linear protein with a single transmembrane domain that is a member of the cytokine receptor superfamily (see Chapter 3). The receptor has tyrosine kinase activity, and it activates a cascade of serine and threonine kinases, resulting in inhibited apoptosis of red cells and their increased growth and development.

The principal site of inactivation of erythropoietin is the liver, and the hormone has a half-life in the circulation of about 5 h. However, the increase in circulating red cells that it triggers takes 2 to 3 d to appear, since red cell maturation is a relatively slow process. Loss of even a small portion of the sialic acid residues in the carbohydrate moieties that are part of the erythropoietin molecule shortens its half-life to 5 min, making it biologically ineffective.

**Sources**

In adults, about 85% of the erythropoietin comes from the kidneys and 15% from the liver. Both these organs contain the mRNA for erythropoietin. Erythropoietin can also be extracted from the spleen and salivary glands, but these tissues do not contain the mRNA and consequently do not appear to manufacture the hormone. When renal mass is reduced in adults by renal disease or nephrectomy, the liver cannot compensate and anemia develops.

Erythropoietin is produced by interstitial cells in the peritubular capillary bed of the kidneys and by perivenous hepatocytes in the liver. It is also produced in the brain, where it exerts a protective effect against excitotoxic damage triggered by hypoxia; and in the uterus and oviducts, where it is induced by estrogen and appears to mediate estrogen-dependent angiogenesis.

The gene for the hormone has been cloned, and recombinant erythropoietin produced in animal cells is available for clinical use as epoetin alfa. The recombinant erythropoietin is of value in the treatment of the anemia associated with renal failure; 90% of the patients with end-stage renal failure who are on dialysis are anemic as a result of erythropoietin deficiency. Erythropoietin is also used to stimulate red

cell production in individuals who are banking a supply of their own blood in preparation for autologous transfusions during elective surgery (see Chapter 32).

**Regulation of Secretion**

The usual stimulus for erythropoietin secretion is hypoxia, but secretion of the hormone can also be stimulated by cobalt salts and androgens. Recent evidence suggests that the $O_2$ sensor regulating erythropoietin secretion in the kidneys and the liver is a heme protein that in the deoxy form stimulates and in the oxy form inhibits transcription of the erythropoietin gene to form erythropoietin mRNA. Secretion of the hormone is facilitated by the alkalosis that develops at high altitudes. Like renin

secretion, erythropoietin secretion is facilitated by catecholamines via a -adrenergic mechanism, although the renin–angiotensin system is totally separate from the erythropoietin system

**Recombinant Human Erythropoietin**

When planning to use recombinant human erythropoietin (rHuEPO), the following points must be considered:

1. If the degree of anemia is disproportionate to the degree of thrombocytopenia and neutropenia, this may be due to other causes of low hemoglobin such as hemorrhage, iron deficiency, or hemolysis and these will not be resolved by rHuEPO.
2. Not all patients respond to rHuEPO because of "end-organ" problems, such as myelodysplastic syndrome and some anemias of chronic illness.
3. Patients on cisplatin-containing regimens who suffer renal damage may respond well to rHuEPO.

**Indications**

Thrombotic events have been associated with the use of the various forms of recombinant erythropoietin. In addition, especially in adults, there are data showing a shortening of progression to relapse in patients with various cancers including lymphoma. Any decision to use these drugs should take these factors into account. There are no proven indications for the use of recombinant human erythropoietin in pediatric oncology and concerns exist about appropriate dosing schedule, cost and risk of thrombovascular events. Possible indications in pediatrics include:

- Anemia secondary to renal failure
- Anemia of chronic illness, such as human immunodeficiency virus and juvenile rheumatic arthritis
- Anemia secondary to chemotherapy (to decrease the need for blood transfusions, particularly in children with solid tumors)
- Anemia associated with radiation therapy
- Anemia after allogeneic stem cell transplantation
- Anemia secondary to myelodysplastic syndromes when the serum erythropoietin is low.

Contraindications

1. Anemia secondary to nutritional deficiencies, hemorrhage, or hemolysis.
2. Uncontrollable hypertension.
3. Hypersensitivity to mammalian-cell-derived products or to human albumin

**Dose and Dose Modification Schedule**

1. Obtain baseline serum erythropoietin and ferritin levels prior to starting therapy.
2. If ferritin is low, prescribe ferrous sulfate 6 mg elemental iron/kg/day divided into three daily doses.
3. Start rHuEPO at a dose of 50–100 units/kg/day subcutaneously (SC) three times a week. Darbepoetin alpha is an analog of erythropoietin with a longer plasma half-life and can be used once every 2–4 weeks. The starting dose is 2.25 µg/kg/dose.
4. If there is no response within 2–4 weeks, increase dose up to 300 Units/kg/day three times a week or the darbepoetin dose to 4.5 µg/kg/week.
5. If the hemoglobin reaches 13 g/dl, discontinue rHuEPO until the hemoglobin is 12 g/dl; then resume at 25% dose.
6. If the hemoglobin increases very rapidly (.1 g/dl in 2 weeks) or hemoglobin reaches 12 g/dl, reduce the dose by 25%.
7. Give rHuEPO concurrently with chemotherapy.
8. Continue rHuEPO until the patient no longer requires red cell support.

Early initiation (prior to the need for transfusions), a low observed or predicted erythropoietin level (,0.825) and evidence of early response (more than 1 g/dl rise in hemoglobin within the first 4 weeks) are all associated with increased likelihood of response. Patients meeting all three of these criteria show an 85% chance of significant response (more than 2 g/dl rise in hemoglobin). Almost all of these patients have renal-failure-associated anemia and were treated with subcutaneous erythropoietin.

**Adverse Reactions**

1. Common: hypertension, pain at the injection site, headache, fever, diarrhea.
2. Uncommon: nausea, malaise, seizures, thrombosis. There are reports of pure red cell aplasia due to neutralizing antibodies during erythropoietin treatment