Agents Used in Anemias

Hematopoiesis requires a constant supply of: 1. Essential elements: Iron, vitamin B12 and folic acid. 2. Hematopoietic GF.

	Info.	Disease and cause	Therapy indications	Treatment or Drugs	About The Drug	Side Effects
IRON	* Iron deficiency is the most common cause of chronic anemia and causes microcytic hypochromic anemia. **Pharmacokinetics of Iron** ■ Free iron is toxic. ■ All iron used to support hematopoiesis is reclaimed from catalysis of hemoglobin in senescent or damaged erythrocytes. ■ Only a small amount of iron is lost from the body. **Possibile causes of Iron Deficiency:** ■ Increased iron requirements ■ Increased iron losses. **Absorption:** ■ Daily intake: 10-15mg of elemental iron. ■ Heme iron in meat hemoglobin and myoglobin is absorbed intact. ■ Iron from other sources is tightly bound to organic compounds and is less available and should be reduced to ferrous iron before it can be absorbed. ■ Daily absorption: 5-10% of the daily intake, usually from duodenum and proximal jejunum. ■ Absorption can increase in response to low iron or increased requirements. ■ Divalent Metal Transporter (DMT1) actively transports ferrous iron across the luminal membrane of intestine. ■ Regulated by mucosal cell iron stores. ■ Ferroportin1(IREG1), transports iron across the basolateral membrane into the blood. ■ Excess iron is stored in the mucosa as ferritin, (a water-soluble complex consisting of a core of ferric hydroxide covered by a shell of specialized protein called apoferritin). **Transport:** ■ Transferrin (Tf) binds two molecules of iron in the plasma. ■ The complex binds to Transferrin Receptors (TfR) on the maturing erythroid cells which internalize the complex through the process of receptormediated endocytosis.	**Iron deficiency.** **Causes:** *Increased iron requirements *Increased iron losses.	* Treatment and prevention of iron deficiency anemia: 1. Increased requirements: infants, children, pregnant and lactating women, patients on hemodialysis, patients on erythropoietin treatment. 2.Inadequate iron absorption: after gastrectomy, severe small bowel disease. 3.Blood loss: acute or chronic, most common cause of iron deficiency anemia.	***Oral Iron Preparations:** **-Ferrous sulfate.** **-Ferrous gluconate.** **-Ferrous fumarate.**	All are effective and inexpensive.	Can cause nausea, epigastric discomfort, cramps, constipation or diarrhea and black stools.
				***Parenteral Iron Therapy:**	Reserved for patients with documented iron deficiency who are unable to tolerate or absorb oral iron and for patients with extensive chronic blood loss who can not be effectively maintained with oral iron alone.	–Carry the risk of iron overload.
				1.**Iron dextran:** Given by deep IM injection or IV infusion.		– IM injection causes local pain and tissue staining. – IV infusion causes hypersensitivity reactions: headache, fever, arthralgia, N, V, back pain, flushing, bronchospasm and rarely anaphylaxis and death.
				2.**Iron-sucrose complex:**		
				3.**Iron sodium gluconate:** (only IV)		less likely to cause hypersensitivity
		Acute Iron Toxicity. Cause: Usually results from accidental ingestion by children as well as parenteral iron. -10 tablets can be lethal in children. **Symptoms:** -Necroticzing gastroenteritis: vomiting, pain, bloody		**Deferoxamine ” Desferal”**	Is a potent iron-chelating compound which binds already absorbed iron and promotes its excretion in urine and feces.	
				Whole Bowel Irrigation	To flush out unabsorbed pills.	
				Activated charcoal	Ineffective	

	■ Iron is released for hemoglobin synthesis. ■ Transferrin- transferrin receptor complex is recycled to the plasma membrane and transferrin dissociates and returns to the plasma. **Storage:** ■Ferritin(apoferritin AF and iron) is the storage form of iron. ■Stored in intestinal mucosa and in macrophages in the liver, spleen, and bone. ■Ferritin in serum is in equilibrium with storage ferritin and can estimate body iron stores. **Elimination:** ■ There is no mechanism for excretion. ■ Small amounts are lost by exfoliation of intestinal mucosal cells, bile, urine and sweat.	diarrhea, shock, lethargy and dyspnea. -Patients may improve but may proceed to metabolic acidosis, coma and death.		**Supportive therapy**	Also necessary.	
		Chronic Iron Toxicity (Hemochromatosis) **Symptoms:** Excess iron can deposit in the heart, liver, pancreas, and other organs leading to organ failure.	For Chronic iron toxicity which usually occurs in: 1. Inherited Hemochromatosis: excessive iron absorption. 2. Patients with frequent transfusions e.g. in patients with September hemolytic anemias. .	**Intermittent phlebotomy** (الفصد		
				Deferoxamine	much less efficient than phlebotomy.	
				Deferasirox ” Exjad e”	oral, more convenient than deferoxamine.	
Vit. B12	■ Porphyrin-like ring with a central cobalt atom. ■ Meat, liver, eggs, and dairy products. ■ Nutritional deficiency only occurs in strict vegetarians. ■ Daily requirement : 2mcg ■ Storage pool: 300-5000mcg. ■ It would take about 5 years to exhaust all the stored pool and for megaloblastic anemia to develop after stopping absorption. **Pharmacokinetics of Vitamin B12** ■ Absorption requires the complexing with the: Intrinsic Factor(Castle’s Factor), which is a glycoprotein secreted by the parietal cells of the stomach. ■ Transported in the body by Transcobalamine <u>II. Schilling’s Test: – Measures absorption and urinary excretion of radioactively labeled Vitamin B12.</u> **Actions of Vitamin B12** 1. Transfer of a methyl group from N5-methyltetrahydrofolate to homocysteine, forming methionine. N5-methyltetrahydrofolate is the major dietary and storage folate. 2. Conversion of N5-methyltetrahydrofolate to tetrahydrofolate. Deficiency leads to accumulation of N5- methyltetrahydrofolate cofactors and depletion of tetrahydrofolate . Megaloblastic anemia of Vitamin B12 deficiency can be partially corrected by ingestion of large amounts of folic acid. This is because folic acid can be reduced to dihydrofolate by the enzyme dihydrofolate reductase. 3. Isomerization of methylmalonylCoA to succinyl-CoA by the enzyme methylmalonyl-CoA mutase. Vitamin B12 depletion leads to the accumulation of methylmalonyl-CoA , thought to cause the neurological manifestations of Vitamin B12 deficiency.	**Deficiency**: **Pernicious anemia.**	Vit. B12 defeciency caused by: Distal ileal disease e.g. Inflammation or resection or Diphyllobothrium latum infestation. Bacterial overgrowth of the small intestine. Chronic pancreatitis. Thyroid disease. Congenital deficiency of the intrinsic factor. Congenital selective Vitamin B12 malabsorption !!! (may be in Jordan)	**Methylcobalamine Deoxyadenosyl cobalamine Cyanocobalamine. Hydroxocobalamine**		
				Parenteral Life-long treatment.	Daily or every other day for 1-2 weeks to replenish the stores. Maintenance: injections every 1-4 weeks.	
				Oral	Only for patients who refuse or can not tolerate injections.	
				Intranasal	For patients in remission	

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<td>Folic Acid</td>
<td>■ Reduced forms of folic acid are required for the synthesis of amino acids, purines and DNA. ■ Deficiency is common but easily corrected.
Chemistry of Folic Acid
■ Folic acid=Pteridine+ PABA+ Glutamic acid. ■ Folic acid is reduced to Di and Tetra hydrofolate and then to folate cofactors, which are interconvertible and can donate one-carbon units at various levels of oxidation. ■ In most cases folic acid is regenerated.
Kinetics of Folic Acid
■ Readily and completely absorbed from the terminal jejunum. ■ Glutamyl residues are hydrolyzed before absorption by α-1-glutamyltransferase (Congugase), within the brush border of the mucosa. ■ N5-methyltetrahydrofolate is transported into the blood stream by active and passive processes. ■ Widely distributed in the body. ■ Inside cells, it is converted into THF by demethylation reaction in the presence of Vitamin B12. ■Only 5-20 mcg are stored in the liver. ■ Excreted in urine and stool and also destroyed by catabolism. ■ Megaloblastic anemia can develop within 1-6 months after stopping intake. ■ Present in yeast, liver, kidney and green vegetables.
Actions of Folic Acid
■ THF cofactors are important in onecarbon reactions: –Production of dTMP from dUMP, which is needed in DNA synthesis. – Generation of methionine from homocysteine. – Synthesis of essential purines. Deficiency can result in: Megaloblastic anemia. Congenital malformations. Occlusive Vascular disease due to elevated homocysteine.</td>
<td>Deficiency</td>
<td>Megaloblastic Anemia of Folic Acid Deficiency caused by:
- Inadequate dietary intake.
-Alcoholism, due to neglected nutrition.
-Liver disease causing impaired hepatic storage.
-Pregnancy and hemolytic anemia which increase the demand.
-Malabsorption syndrome.
-Renal dialysis.
-Drugs: Methotrxate, Trimethoprim and Phenytoin.</td>
<td>Parenteral administration</td>
<td>Rarely necessary because it is well absorbed orally even in malabsorption.</td>
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<td>Oral</td>
<td>-1 mg daily until cause is corrected.
-Or, indefinitely for patients with malabsorption or dietary inadequacy.
-Can be given prophylactically.
-Routinely given in early pregnancy or even before being pregnant.
-Recently supplemented to foods.</td>
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<td colspan="7">Hematopoietic Growth Factors :
1.Erythropoietin (Epoetin alfa). 2.Colony Stimulating Factors. 3.Granulocyte colony-stimulating factor(G-CSF). 4.Granulocyte-macrophage colonystimulating factor (G-CSF). 5.Interleukin-11 (IL-11). 6.Thrombopoietin.
* Regulate the proliferation and differentiation of hematopoietic progenitor cells in the bone marrow.
* Useful in hematologic as well as nonhematologic conditions, potential anticancer and antiinflammatory drugs.</td>
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<td>Erythropoietin (Epoetin alfa).</td>
<td>■ 34-39 kDa glycoprotein.
■ Was the first isolated growth factor.
■ Originally purified from urine of patients with severe anemia.
■ Recombinant human erythropoietin (rHuEPO, or Epoietin alfa) is produced in a mammalian cell expression system.
■ Half-life after iv administration is 4-13 hours.
■ It is not cleared by dialysis.
■ Darbepoetin alfa has longer half life.
■ Produced in the kidney in response to hypoxia through increased rate of transcription of the gene .
■ Needs active bone marrow (no deficiency, no primary bone marrow disease and no suppression by drugs or chronic diseases).</td>
<td>Deficiency</td>
<td>1. Anemia of chronic renal failure:
– These are the patients most likely to benefit from treatment.</td>
<td>– 50-150 IU/kg IV or SC three times a week.</td>
<td>– Failure to respond is usually due to iron or folic acid deficiency.</td>
<td rowspan="2">Toxicity of Erythropoietin
*Due to rapid increases in hematocrit and hemoglobin: hypertension and thrombotic complications.
*Allergic reactions are infrequent and mild.</td>
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<td>2. Primary bone marrow disorders and secondary anemias:
aplastic anemia, myeloproliferative and myelodysplastic disorders, multiple myeloma and bone marrow malignancies.

Also anemia of chronic inflammation, AIDS and cancer.</td>
<td>– Patients require higher doses(100-500 IU/kg).</td>
<td>– Response is better with low baseline erythropoietin levels.

– Response is generally incomplete.</td>
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		■ Normal serum level 20 IU/L. ■ Elevated in most of anemias (up to thousands) but lowered in anemia of chronic renal failure. **Functions:** ■ Stimulates erythroid proliferation and differentiation by interacting with specific receptors(JAK/STAT cytokine receptor) on red cell progenitor. ■ Releases reticulocytes from the bone marrow.		3. Anemia of zidovudine treatment. 4. Anemia of prematurity. 5. After phlebotomies for autologous transfusion for elective surgery. 6. Iron overload. 7. Unethically, used by athletes.				
Myeloid Growth Factors	**G-CSF**	■ Works on(JAK/STAT receptors. **Functions:** ■ Stimulates proliferation and differentiation of progenitors committed to the neutrophil lineage. ■ Activates the phagocytic activity of mature neutrophils and prolongs their survival in the circulation. ■ Mobilizes hemopoietic stem cells into the peripheral circulation.	**Deficiency**	**1.Cancer Chemotherapy-Induced Neutropenia:** ■Granulocyte transfusion is not practical. ■G-CSF accelerates neutrophil recovery, leading to reduced episodes of febrile neutropenia, need for antibiotics and days of hospitalization , but do not improve survival. ■G-CSF is reserved for risky patients. ■GM-CSF can produce fever on its own. ■They are safe even in the post chemotherapy supportive care of patients with AML. **2. Congenital neutropenia.** **3.Cyclic neutropenia.** **4.Myelodysplasia.** **5.Aplastic anemia.** **6.Autologous Stem Cell Transplantation:** – High dose chemotherapy regimens produce extreme myelosuppression, which is counteracted by reinfusion of the patient's own hematopoietic stem cells which are collected before the chemotherapy. **7. Allogenic Bone Marrow Transplantation.** **8. Mobilization of peripheral blood stem cells (PBSCs). –** Patients or donors are given GM-CSF for 4 days, then leukapheresis, CD34 is used as a marker for the stem cells. At least 5x106 CD34 cells/kg should be reinfused to ensure effective engraftment.	Originally purified from cultured human cells.	**rHuG-CSF (Filgrastim) 1991**	– Produced in a bacterial cell expression system. – 175 amino acids, 18 kD mol. wt. – Has a half life of 2-7 hours. – **Pegfilgrastim= Filgrastim** covalently conjugated with polyethylene glycol. Injected once per chemotherapy cycle.	**Toxicity of Myeloid Growth Factors:** *Bone pain. *Fever, malaise, arthralgia, myalgia. *Capillary Leak Syndrome: peripheral edema, pleural or pericardial effusions. *Allergic reactions. *Splenic rupture.
	GM-CSF	■Has broader actions. Also works on JAK/STAT receptors. **Functions:** ■Stimulates proliferation and differentiation of early and late granulocytic progenitor cells as well as erythroid and megakaryocyte progenitors. ■With interleukin-2, also stimulates T-cell proliferation. ■Locally, it is an active factor of inflammation. ■Mobilizes peripheral blood stem cells, but less than G-CSF.				**rHuGM-CSF (Sargramostim)**	– Produced in a yeast cell expression system. – 127 amino acids, 15-19 kD mol. wt. – Has a half life of 2-7 hours.	

Megakaryocyte Growth Factors	**Interleukin-11 (IL-11)**	■65-85 kDa protein. ■Produced by fibroblasts and stromal cells in the bone marrow. ■Half life is 7-8 hours after sc injection. ■Acts through a specific receptor. **Functions:** ■Stimulates the growth of multiple lymphoid and myeloid cells. ■Stimulates the growth of primitive megakaryocytic progenitors. ■Increases the number of peripheral platelets and neutrophils.	**Deficiency**	*** Thrombocytopenia** Platelets transfusion is an alternative. Approved for the secondary prevention of thrombocytopenia in patients receiving cytotoxic chemotherapy for treatment of nonmyeloid cancers *** Does not appear to have an effect on leukopenia caused by myelosuppressive chemotherapy.**	**Oprelvekin**	– Is the recombinant form. – Produced by expression in E.coli. – Given by SC injection, 50mcg/kg/day for 2-3 weeks after chemotherapy. Or, until platelet count rises to	**Toxicity:** * Fatigue, headache, dizziness, anemia, dyspnea, transient atrial arrhythmias and hypokalemia.
	Thrombopoietin	■It is still an investigational agent. ■65-85 kDa glycoprotein. ■Recombinant form is produced by expression in human cells. **Functions:** ■Independently stimulates the growth of primitive megakaryocytic progenitors. ■Also stimulates mature megakaryocytes. ■Activates mature platelets to respond to, ■inducing stimuli.					

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