**ASPHO Board Questions - Nutritional Anemias (2021 items)**

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1. Which of the following best characterizes the function of ferroportin in iron metabolism?
2. A form of storage iron in intestinal mucosal cells
3. A transport protein in the plasma
4. A receptor protein on the surface of erythroid progenitors
5. Transmembrane iron exporter
6. A form of storage iron in hepatic cells

**Explanation**

The correct answer is D. Ferroportin is the only known iron exporter and is found predominantly, though not exclusively, on enterocytes and reticuloendothelial macrophages. Iron is stored in the tissues as ferritin or hemosiderin, so options A and E are incorrect. Transferrin (option B) binds and transports two atoms of ferric iron (Fe+++) from the intestinal mucosal cell or other sites to erythroid marrow, where it binds to membrane-bound transferrin receptors (option C).

1. A 20-month-old otherwise healthy male presents late for his 18-month well child check. During his first year of life, he took iron-fortified formula and had a point-of-care hemoglobin (Hgb) of 12 g/dL at his 1-year well child check. His mother reports that he is a picky eater but loves milk and has recently become obsessive about chewing the corners of his cardboard books. Physical examination is normal except for a flow murmur. Which combination of laboratory test results listed below would most likely characterize this patient?

A. Hgb 8.7 g/dL, mean corpuscular volume (MCV) 60 fL, serum ferritin 2 ng/mL

B. Hgb 12.0 g/dL, MCV 80 fL, serum ferritin 30 ng/mL

C. Hgb 9.2 g/dL, MCV 60 fL, serum ferritin 30 ng/mL

D. Hgb 11.2 g/dL, MCV 90 fL, serum ferritin 7 ng/mL

E. Hgb 9.8 g/dL, MCV 68 fL, serum ferritin 50 ng/mL

**Explanation**

The correct answer is A. Young children who drink excessive cow’s milk are at risk for nutritional iron deficiency anemia. In children who previously received iron-fortified formula, the risk is highest during the second year of life after transition to cow’s milk. Iron stores initially become depleted, followed by iron-deficient erythropoiesis and finally frank anemia. Children with iron-deficiency anemia have low serum ferritin, therefore options B, C, and E are incorrect. Iron-deficiency anemia results in a microcytic anemia (low mean corpuscular volume), so answer D is incorrect.

1. Assuming that adherence has been excellent, which of the following should have returned to normal 6 weeks following appropriate oral iron treatment for a child with severe dietary iron deficiency (hemoglobin [Hgb] 5.0 g/dL and mean corpuscular volume [MCV] 48 fL at the beginning of therapy)?

A. Hgb concentration

B. MCV

C. Red cell distribution width

D. Peripheral blood smear

E. Serum ferritin

**Explanation**

In uncomplicated nutritional iron deficiency, the hemoglobin (Hgb) concentration (option A) virtually always returns to the normal range within 6 weeks. The rate of Hgb rise often is quite dramatic. The mean corpuscular volume (MCV; option B) takes 3 months or so to return to normal. The red cell distribution width (RDW; option C) actually increases for the first 8 weeks following iron treatment as a result of a young population of large, well-hemoglobinized erythrocytes accompanying the older hypochromic microcytic cells from the iron-deficient state. The peripheral blood film (option D), like the RDW and MCV, does not return to normal for 2 to 3 months. Serum ferritin (option E) is the last parameter to normalize.

1. Which of the following laboratory test values is reduced in iron deficiency?

A. Serum transferrin

B. Free erythrocyte protoporphyrin (FEP) or Zinc protoporphyrin (ZPP)

C. Soluble transferrin receptor

D. Reticulocyte iron content (CHr)

E. Absorption of iron following an oral dose of iron

**Explanation:** Reticulocyte iron content may be the most sensitive early hematologic indicator of iron deficiency, usually noted before any changes in the blood count. Serum transferrin, FEP/ZPP, soluble transferrin receptor, and iron absorption all are increased in the setting of iron deficiency.

1. Iron-refractory iron deficiency anemia (IRIDA) is a rare inherited condition characterized by congenital iron deficiency anemia, poor response to oral iron, and partial but incomplete response to intravenous iron therapy. Which is the genetic mutation associated with IRIDA?

A. *TFR2*

*B. H63D*

*C. TMPRSS6*

*D. EPOR*

*E. C282Y*

**Explanation**

In patients with IRIDA, mutations in *TMPRSS6* (option C) disrupt the “iron sensor” and result in inappropriately high levels of hepcidin, even in iron deficiency. The constitutively elevated hepcidin results in iron-restricted erythropoiesis by impaired release of iron into the plasma from both duodenal enterocytes and RE macrophages. Hepcidin exerts its effect on these cells by binding and degrading ferroportin, the only known cellular iron exporter; therefore, there is no “pump” to bring iron into the plasma, where it is then bound to transferrin. *TFR2, H63D,* and *C282Y* (options A, B, and E) are all mutations that result in hereditary hemochromatosis. *EPOR* (option D) is a mutation of the erythropoietin receptor that results in primary erythrocytosis.

1. Which of the following is a physiologic role of hepcidin in iron homeostasis?

A. It enhances iron absorption from intestinal mucosal cells.

B. It inhibits the production of interleukin-6 (IL-6) by macrophages and T-cells.

C. It enhances the oxidation of ferrous to ferric iron to facilitate iron binding to transferrin.

D. It inhibits iron release from macrophages.

E. It is a form of storage iron in hepatic parenchymal cells.

**Explanation:** Hepcidin is a small peptide made in the liver that appears to have an antiinflammatory function. Its production is induced by IL-6 but does not inhibit it. Its role in iron metabolism is to block iron transport from intestinal mucosal cells and macrophages by binding to and degrading ferroportin. It is a key mediator in the pathogenesis of anemia of inflammation (chronic disease). Answer D accordingly is the only correct answer that makes sense.

1. A 10-year-old healthy male is referred to you for a family history of hemochromatosis in his father. A recent copy of the father’s laboratory studies include transferrin saturation (TfSat) of 98% (normal range, 20%-50%) and a serum ferritin of 3,548 mcg/L (normal range, 18-200 mcg/L). In hereditary hemochromatosis, what is the most common genetic mutation?

A. TFR2

B. H63D

C. FPN1

D. HAMP

E. C282Y

**Explanation:**

The C282Y *HFE* mutation is the most common cause of hereditary hemochromatosis (option E). H63D (option B) is another mutation in the *HFE* gene but is less common than C282Y. TFR2, FPN1, and HAMP (options A, C, and D) are other, more rare forms of hereditary hemochromatosis.

1. You are referred a 3-year-old boy with erythrocytosis. Upon further questioning, it appears there are other affected family members including one of three other siblings living in the same house and several other cousins in their native country. The boy has very low levels of plasma erythropoietin and no splenomegaly. What is the most likely cause of this erythrocytosis?

A. Mutant hemoglobin having high oxygen affinity

B. Low levels of red cell 2,3-DPG due to an inactivating mutation of DPG mutase

C. Mutation of Epo receptor causing constitutive signaling

D. Carbon monoxide poisoning

E. Inactivating mutation of gene encoding von Hippel Lindau (vHL) protein

**Explanation:** High oxygen affinity hemoglobin (Hgb) variants result in elevated erythropoietin levels with normal PO2 and SaO2. Similarly low 2,3-DPG levels increase Hgb oxygen affinity and would result in elevated erythropoietin levels. Mutations in the hypoxia sensing pathway (eg, vHL gene mutations [Chuvash polycythemia], proline hydroxylase 2 [PHD2] loss-of-function mutations, and HIF-2 alpha [gain-of-function] mutation) also result in elevated erythropoietin.

Carbon monoxidepoisoning CO binds to the heme moiety thereby allosterically inhibiting oxygen release in tissues and shifting the oxyhemoglobin dissociation curve left. Also, although multiple family members are affected, some live outside the same house. Primary erythrocytosis includes inherited mutations leading to a constitutive RBC production independent of erythropoietin and includes rare autosomal dominant EpoRc mutations with constitutive positive signaling. The myeloproliferative neoplasm polycythemia vera is the most common acquired primary erythrocytosis; however, it very uncommon in children and especially if there is no associated splenomegaly.

1. Which of the following patients presenting with anemia *does not* have appropriate indications to consider intravenous iron therapy?
2. Dialysis-dependent chronic kidney disease
3. New diagnosis nutritional iron deficiency anemia
4. Crohn’s disease, not in remission
5. Iron refractory iron deficiency anemia
6. History of total parenteral nutrition dependence due to intestinal failure

**Explanation**

Standard of care initial therapy for patients with nutritional iron deficiency anemia is oral iron supplementation, typically with an iron salt such as ferrous sulfate (option B). The majority of intravenous iron preparations are approved for utilization in patients with chronic kidney disease (option A). Children with inflammatory bowel disease with active inflammation often have concomitant iron deficiency due to gastrointestinal blood loss. Inflammation results in upregulation of hepcidin, which inhibits oral iron absorption, and is best treated with intravenous iron therapy. Similarly, children with intestinal failure may have iron malabsorption and poor tolerance of oral iron because of gastrointestinal side effects. Finally, patients with iron refractory iron deficiency anemia have elevated hepcidin levels and limited to no response to oral iron therapy. They have a blunted response to intravenous iron therapy, though the response may be better with larger doses.

1. A 1-year-old, exclusively breastfed infant of a vegan mother presents with progressive pancytopenia and loss of milestones. You suspect cobalamin deficiency. Which laboratory and peripheral smear findings are most consistent with this diagnosis?
2. Normal methylmalonic acid, elevated homocysteine, hypersegmented neutrophils, elevated mean corpuscular volume (MCV)
3. Elevated methylmalonic acid, elevated homocysteine, hypersegmented neutrophils, low MCV
4. Elevated methylmalonic acid, elevated homocysteine, hypersegmented neutrophils, normal MCV
5. Elevated methylmalonic acid, elevated homocysteine, hypersegmented neutrophils, elevated MCV
6. Elevated methylmalonic acid, normal homocysteine, hypersegmented neutrophils, elevated MCV

**Explanation**

Patients with cobalamin deficiency have elevations in both methylmalonic acid and homocysteine due to its role as a coenzyme in the conversion of succinyl-coenzyme A (CoA) to methylmalonyl CoA and homocysteine to methionine. Defective DNA synthesis results in ineffective erythropoiesis, which includes the development of a megaloblastic anemia that includes large red blood cells (elevated mean corpuscular volume) and hypersegmented neutrophils.

1. Which of the following lists the organs involved in fetal erythropoiesis in chronological order?
2. Yolk sac, liver, spleen, bone marrow
3. Yolk sac, spleen, liver, bone marrow
4. Yolk sac, liver, bone marrow, spleen
5. Liver, yolk sac, spleen, bone marrow

**Explanation**

Within the first 6 weeks of gestation, fetal erythropoiesis occurs in the yolk sac. At approximately 6 to 8 weeks, erythropoiesis begins in the liver and continues into the early post-natal period. Erythropoiesis occurs between 3 to 6 months of age in the spleen. Bone marrow erythropoiesis begins around 4 months of age and progressively increases, becoming the predominant source of red blood cells in the third trimester.

1. Which of the following *is not* included in the differential diagnosis of a 5-year-old child presenting with mild, normocytic anemia?
2. Strep pharyngitis (anemia of inflammation)
3. Hypothyroidism
4. Chronic kidney disease
5. Thalassemia trait
6. Statistical anemia

**Explanation**

Thalassemia trait results in a mild, microcytic anemia, typically with an elevated RBC count. Patients with thalassemia trait do not have a normal mean corpuscular volume; therefore, option D is incorrect. The other diagnoses may present with a mild, normocytic anemia. Patients with acute inflammation or infection may have a mild anemia (option A). Chronic inflammation may progress to a microcytic anemia due to prolonged iron-restricted erythropoiesis. Hypothyroidism and chronic kidney disease (options B and C) may result in a normocytic anemia. Patients may have a history of poor growth or other nonspecific symptoms. Statistical anemia (option E) is a diagnosis of exclusion but describes the 2.5% of the population that fall below two standard deviations below the normal hemoglobin range.

1. A 14-year-old Greek girl recently has been diagnosed with systemic juvenile rheumatoid arthritis. Which of the following iron studies is most consistent with this clinical presentation?

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Hemoglobin (Hgb) | Mean Corpuscular Voume (MCV) | Transferrin Saturation (TSAT) | Serum Ferritin | Urinary Hepcidin |
| Normal Range | 12.0-16.0 g/dL | 78-102 fL | 20%-50% | 18-200 mcg/dL | 15-200 ng/mg Cr |

A. Hgb 11.8 g/dL, MCV 79 fL, TSAT 25%, ferritin 70 mcg/dL, urinary hepcidin 25 ng/mg Cr

B. Hgb 12.2 g/dL, MCV 82 fL, TSAT 25%, ferritin 70 mcg/dL, urinary hepcidin 25 ng/mg Cr

C. Hgb 11.8 g/dL, MCV 79 fL, TSAT 15%, ferritin 18 mcg/dL, urinary hepcidin 10 ng/mg Cr

D. Hgb 11.8 g/dL, MCV 82 fL, TSAT 15%, ferritin 328 mcg/dL, urinary hepcidin 220 ng/mg Cr

**Explanation:** All of the answer options present very similar RBC indices. Early iron deficiency can be difficult to distinguish from ß-thalassemia trait on the basis of RBC indices alone. Iron studies, hemoglobin electrophoresis, and clinical response to oral iron therapy can assist in making this distinction. The anemia of inflammation can be distinguished from iron deficiency and ß-thalassemia trait by the dissociation of the serum ferritin (high) from the transferrin saturation (low). Like ferritin, hepcidin also is an acute-phase reactant and is increased in inflammatory states. The increase in hepcidin and its effect on iron homeostasis is one of the contributing factors to the anemia of inflammation.

1. As part of an oral iron absorption test, a child with unexplained anemia receives 3 mg/kg oral dose of elemental iron. Serum iron concentration before the iron dose is 30 μg/dL, and 1 hour later the serum iron concentration is 240 μg/dL. What is this child’s most likely diagnosis?

A. Hereditary hemochromatosis

B. Iron deficiency due to reduced dietary iron

C. Iron deficiency due to malabsorption

D. Anemia of inflammation

E. Upregulation of the transferrin receptor

**Explanation**

The baseline serum iron is greatly reduced, and a marked rise follows the oral iron dose. This indicates a diagnosis of iron deficiency and the expected increased absorption seen when it is due to either diminished iron intake or chronic bleeding. The serum iron would rise only minimally if malabsorption or inflammation were present. Patients with hereditary hemochromatosis and other forms of iron overload would have an elevated baseline serum iron concentration. Transferrin has no role in iron absorption.

1. The family of an adolescent female with iron deficiency asks about foods, aside from meat, that have high iron content. Which of the following food groups has the highest concentration of iron?
2. Citrus fruits (oranges, strawberries)
3. Legumes (Lentil beans, chickpeas)
4. Dairy products (cow’s milk)
5. Nuts (walnuts, almonds)
6. Dark chocolate

**Explanation**

Persons who follow restricted diets, including vegetarian and vegan diets, are at higher risk for developing iron deficiency and should be counseled on iron-rich foods that adhere to their diet. Legumes, including lentil beans, black beans, and chickpeas (option B), are good sources of dietary iron. Citrus fruits (option A) are low in iron but have vitamin C, which enhances iron absorption. Dairy products are low in iron. Calcium within dairy products may inhibit iron absorption. Tannins found in nuts and dark chocolate (options D and E) reduce dietary iron absorption.