

Anemias

Supportive module 4 "Essentials of diagnosis, treatment and prevention of major hematologic diseases"

LECTURE IN INTERNAL MEDICINE FOR IV COURSE STUDENTS

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Plan of the lecture

- Definition
- Epidemiology
- Etiology
- Mechanisms
- Adaptation to anemia
- Classification
- Clinical investigation
- Diagnosis
- Treatment
- Prognosis
- Prophylaxis
- Abbreviations
- Diagnostic guidelines



Definition

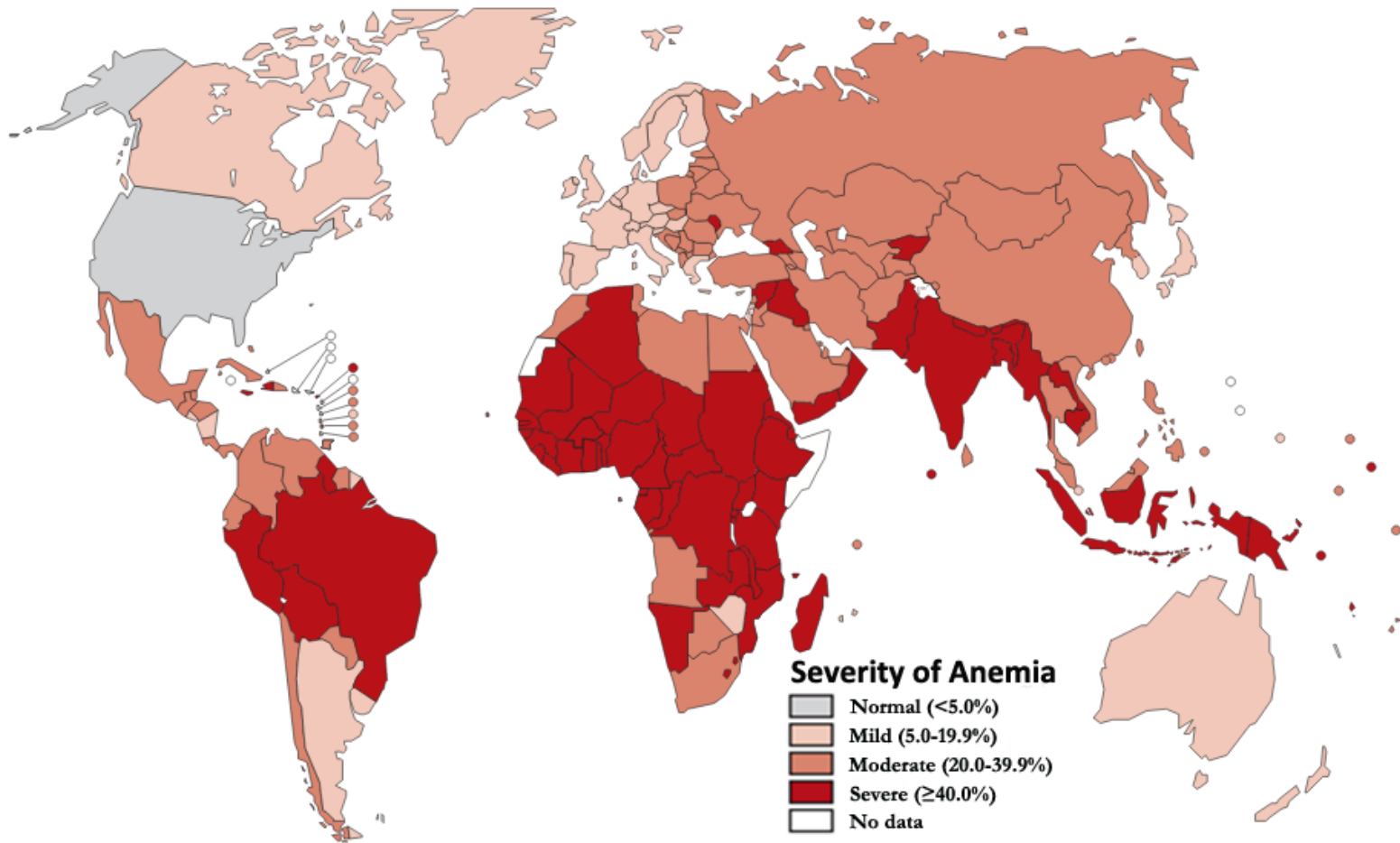
Anemia is a disease and/or a clinical syndrome that consist in lowered ability of the blood to carry oxygen (hypoxia) due to decrease quantity and functional capacity and/or structural disturbances of red blood cells (RBCs) or decrease hemoglobin concentration or hematocrit in the blood

A severe form of anemia, in which the hematocrit is below 10%, is called the hyperanemia

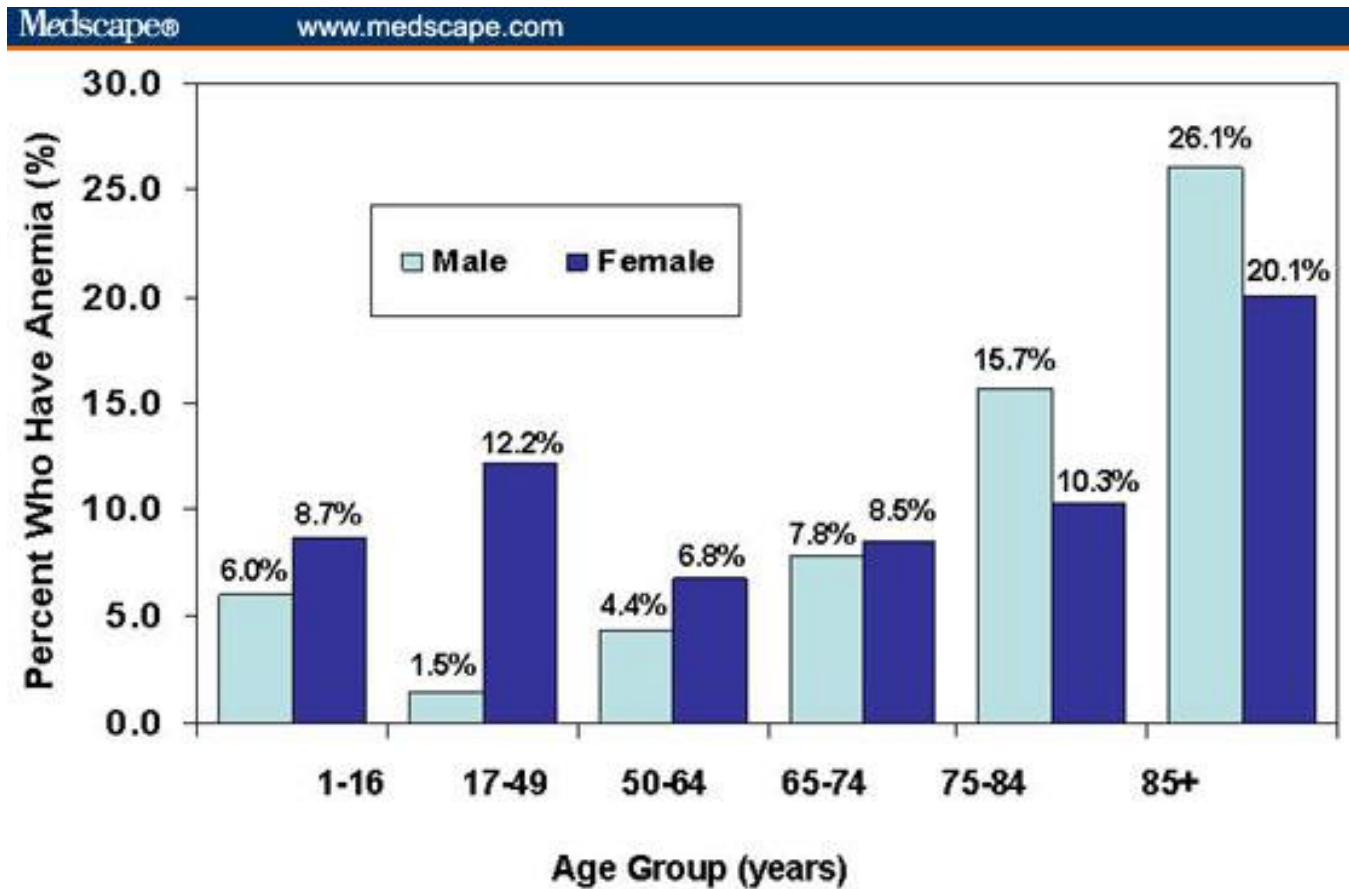
WHO criteria is $Hb < 13 \text{ g/dL}$ in men and $Hb < 12 \text{ g/dL}$ in women (revised criteria for patient's with malignancy $Hb < 14 \text{ g/dL}$ in men and $Hb < 12 \text{ g/dL}$ in women)

Epidemiology 1

Worldwide Prevalence of Anemia, by severity

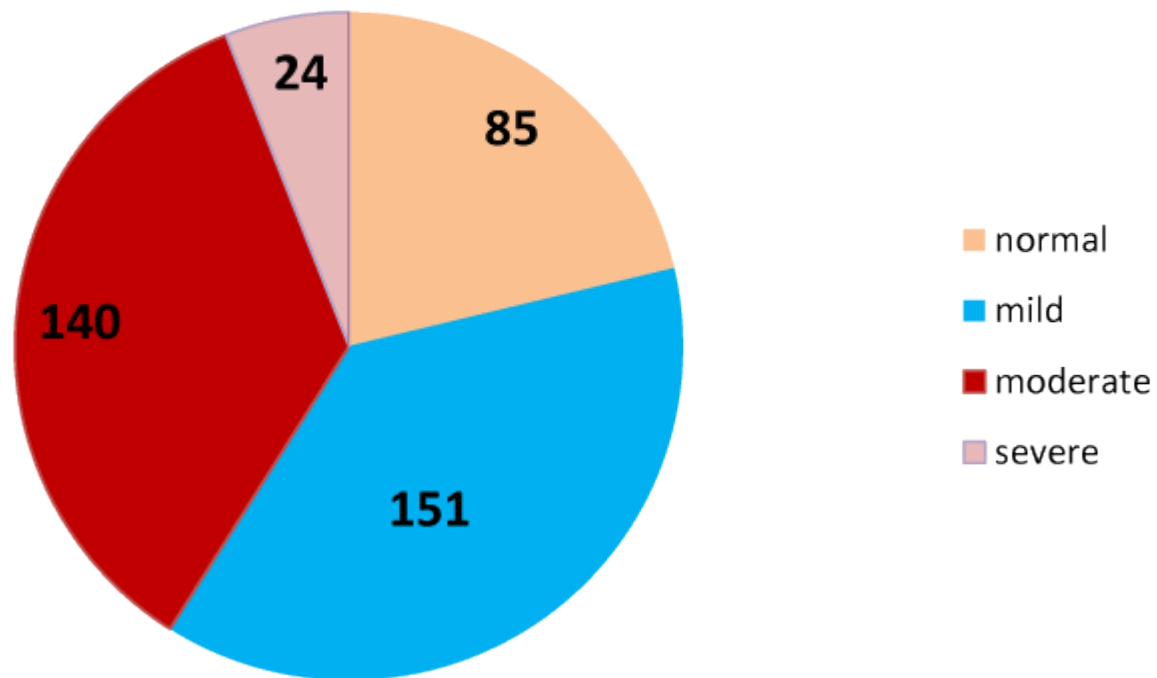


Epidemiology 2



Epidemiology 3

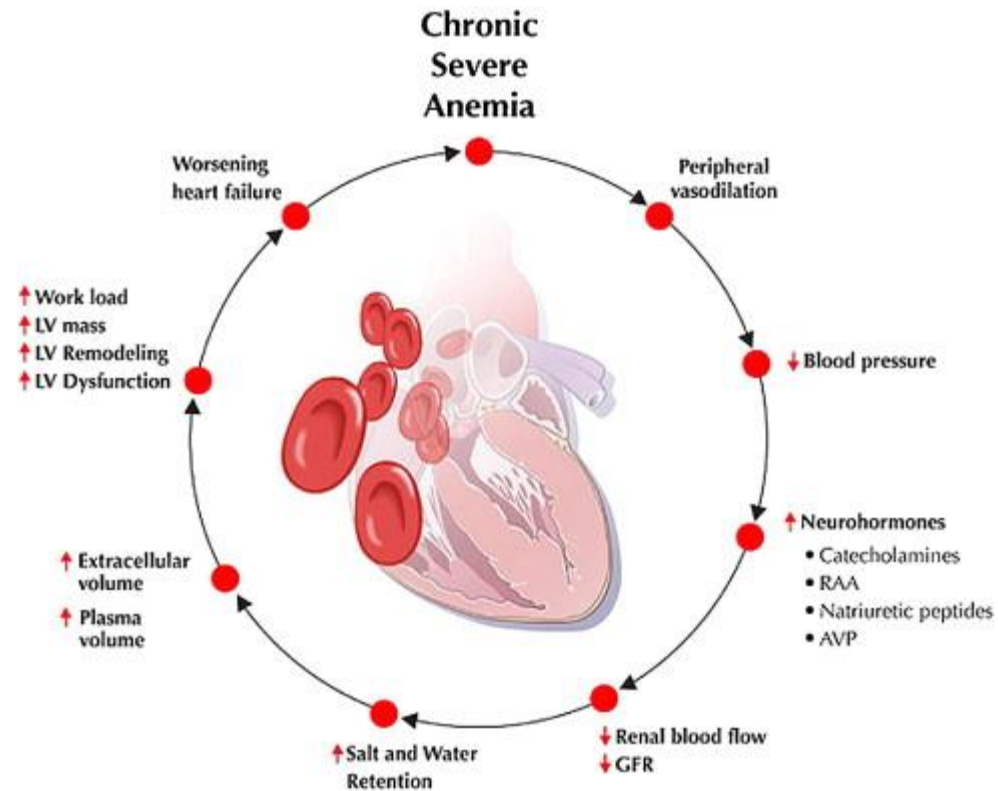
Prevalence of severity of anemia



Etiology 1 (basic forms)

Basic forms

- Blood loss
- Deficient erythropoiesis
- Excessive hemolysis (RBC destruction)
- Fluid overload (hypervolemia)



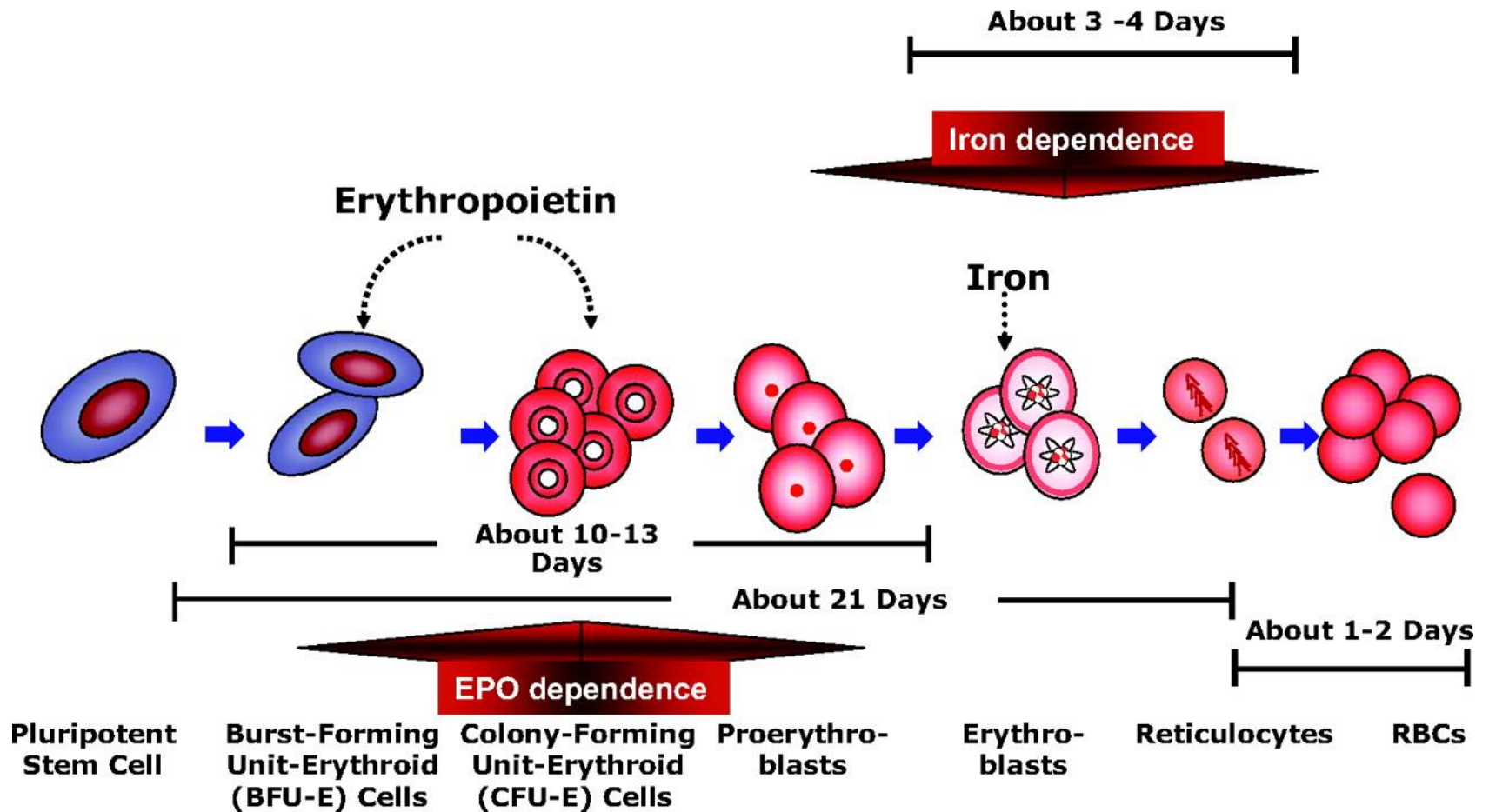
Etiology 2 (blood loss)

- Blood loss can be acute or chronic
- Anemia does not develop until several hours after acute blood loss, when interstitial fluid diffuses into the intravascular space and dilutes the remaining RBC mass
- During the first few hours, however, levels of polymorphonuclear granulocytes, platelets, and, in severe hemorrhage, immature WBCs and normoblasts may rise
- Chronic blood loss results in anemia if loss is more rapid than can be replaced or, more commonly, if accelerated erythropoiesis depletes body iron stores

Etiology 3a (deficient erythropoiesis)

- Deficient erythropoiesis has myriad causes
- Complete cessation of erythropoiesis results in a decline in RBCs of about 7 to 10%/week (1%/day)
- Impaired erythropoiesis, even if not sufficient to decrease the numbers of RBCs, often causes abnormal RBC size and shape

Etiology 3b (deficient erythropoiesis)



Deficient erythropoiesis has myriad causes

USMLE Step 2 CK` test \1

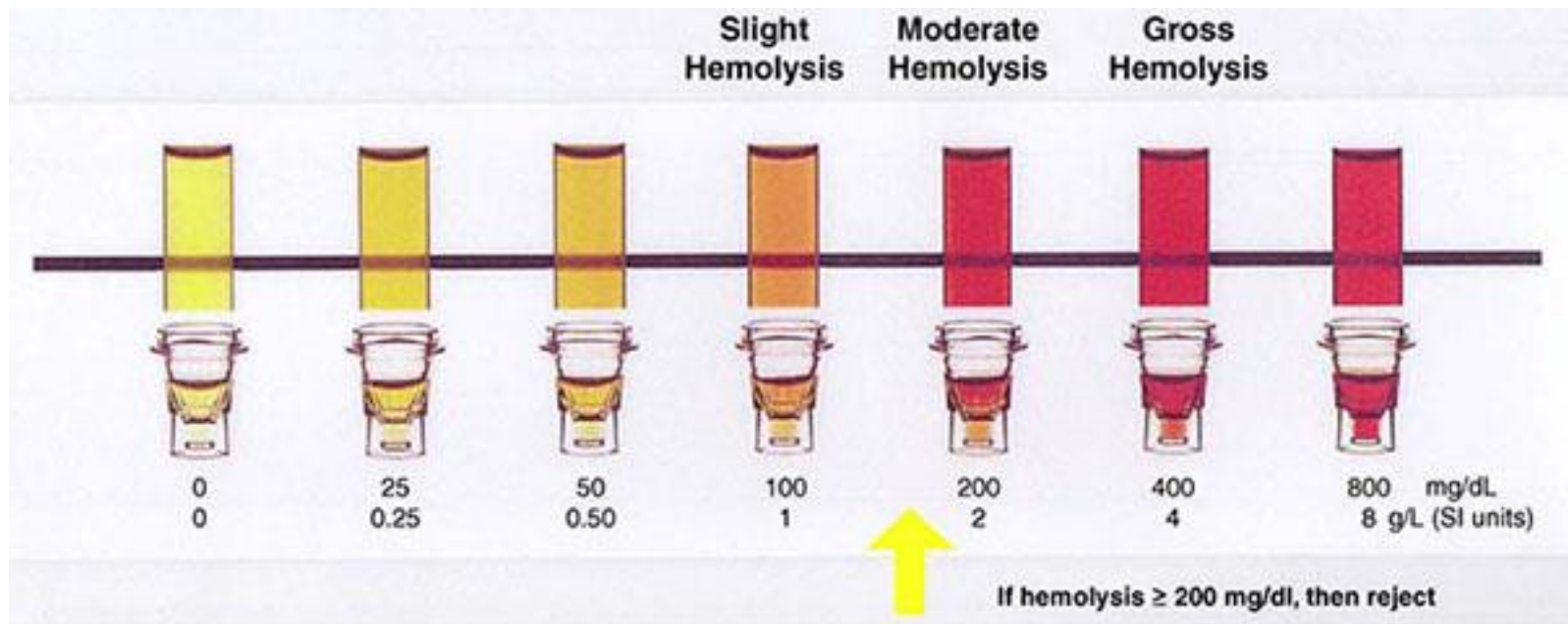
A 32-year-old woman with type 1 diabetes mellitus has had progressive renal failure over the past 2 years. She has not yet started dialysis. Examination shows no abnormalities. Her hemoglobin concentration is 9 g/dL, hematocrit is 28%, and mean corpuscular volume is 94 μm^3 . A blood smear shows normochromic, normocytic cells. Which of the following is the most likely cause?

(A) Acute blood loss (B) Chronic lymphocytic leukemia (C) Erythrocyte enzyme deficiency (D) Erythropoietin deficiency (E) Immuno-hemolysis (F) Microangiopathic hemolysis

Etiology 4a (excessive hemolysis)

- Excessive hemolysis can be caused by intrinsic abnormalities of RBCs or by extrinsic factors, such as the presence of antibodies on their surface, that lead to their early destruction
- An enlarged spleen sequesters and destroys RBCs more rapidly than normal
- Some causes of hemolysis deform as well as destroy RBCs
- Excessive hemolysis does not normally decrease reticulocyte production unless iron or other essential nutrients are depleted

Etiology 4b (excessive hemolysis)



Etiology 5 (Fluid overload (hypervolemia))

- Fluid overload causes decreased hemoglobin concentration and apparent anemia:
- General causes of hypervolemia include excessive sodium or fluid intake, sodium or water retention and fluid shift into the intravascular space
- Anemia of pregnancy is induced by blood volume expansion

Etiology 6

(causes of anemia)

- Blood loss
 - Acute
 - Chronic
- Deficient erythropoiesis
 - Microcytic
 - Normochromic-normocytic
 - Macrocytic
- Excessive hemolysis due to extrinsic RBC defects
- Reticuloendothelial hyperactivity with splenomegaly

Etiology 7

(causes of anemia)

- Immunologic abnormalities
- Mechanical injury
- Excessive hemolysis due to intrinsic RBC defects
- Membrane alterations, acquired
- Membrane alterations, congenital
- Metabolic disorders (inherited enzyme deficiencies)
- Hemoglobinopathies

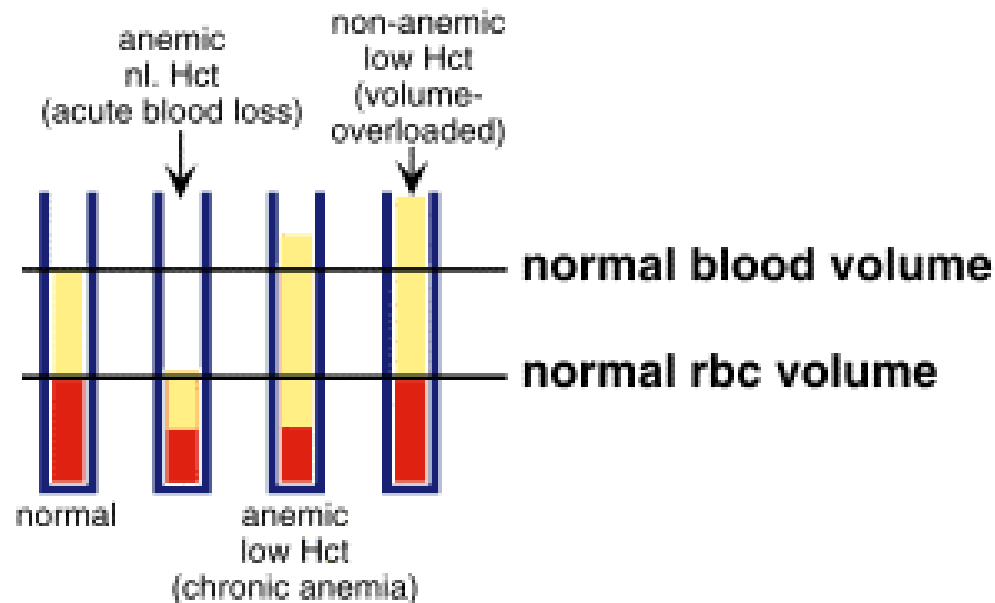
Mechanisms 1a

(anemia due to blood loss)

- With anemia due to blood loss, a reduction in oxygen-carrying capacity occurs along with a decrease in intravascular volume, with resultant hypoxia and hypovolemia
- Hypovolemia leads to hypotension, which is detected by stretch receptors (in the carotid bulb, aortic arch, heart, and lungs) and transmitted by their impulses along afferent fibers of the vagal and glossopharyngeal nerves to the medulla oblongata, cerebral cortex, and pituitary gland

Mechanisms 1b

(anemia due to blood loss)



A person can have a low hematocrit and *not* be anemic

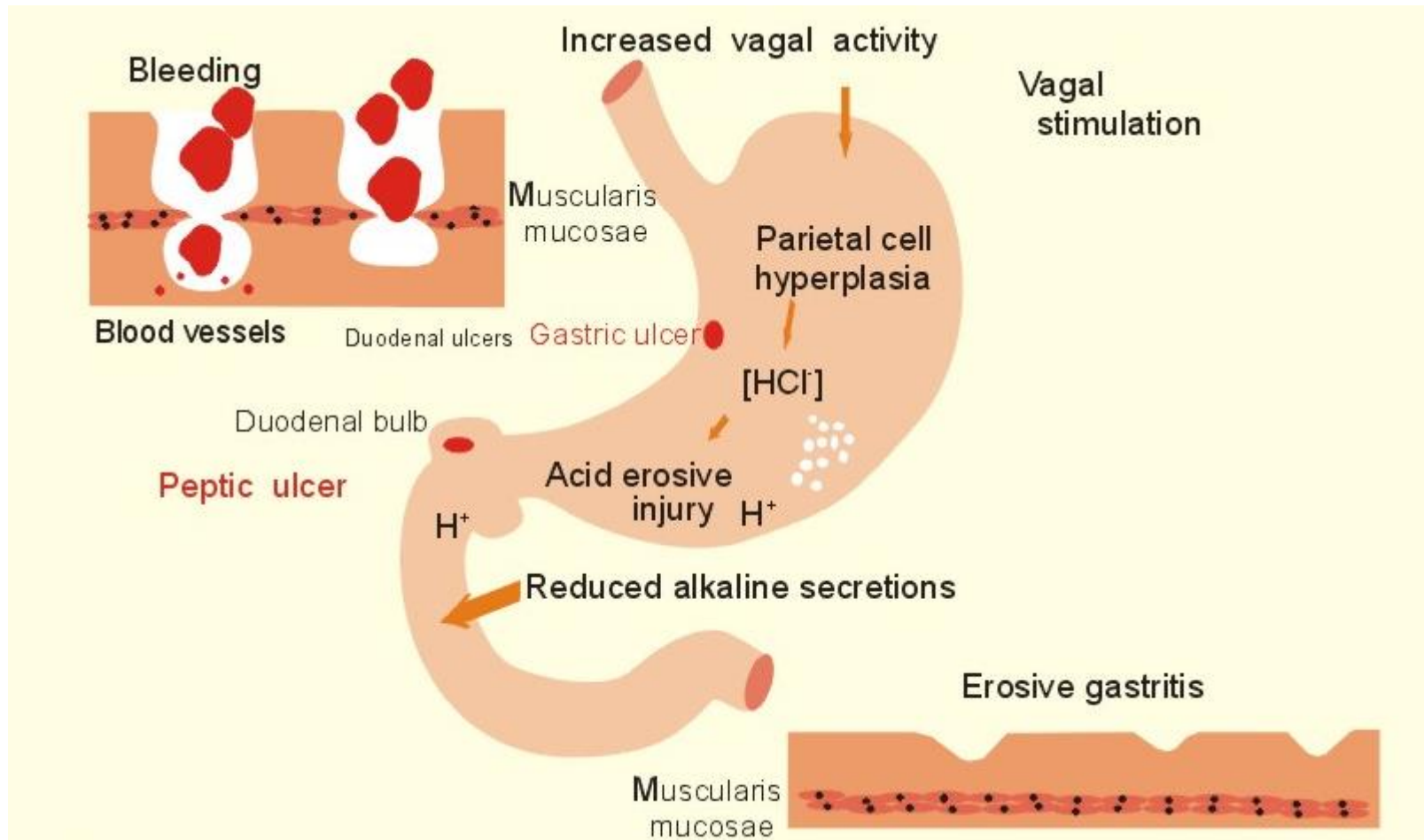
Mechanisms 2a

(anemia due to blood loss)

- In the medulla, sympathetic outflow is enhanced, while parasympathetic activity is diminished
- Increased sympathetic outflow leads to norepinephrine release from sympathetic nerve endings and discharge of epinephrine and norepinephrine from the adrenal medulla
- Sympathetic connection to the hypothalamic nuclei increases antidiuretic hormone (ADH) secretion from the pituitary gland

Mechanisms 2b

(anemia due to blood loss)



Peptic ulcers extend beyond the lamina propria, whereas erosions are superficial

Mechanisms 3

(anemia due to blood loss)

- Antidiuretic hormone (ADH) increases free water reabsorption in the distal collecting tubules
- In response to decreased renal perfusion, juxtaglomerular cells in the afferent arterioles release renin into the renal circulation, leading to increased angiotensin I, which is converted by angiotensin-converting enzyme (ACE) to angiotensin II
- Angiotensin II has a potent pressor effect on arteriolar smooth muscle and stimulates the zona glomerulosa of the adrenal cortex to produce aldosterone

Mechanisms 4

(anemia due to blood loss)

- Aldosterone increases sodium reabsorption from the proximal tubules of the kidney, thus increasing intravascular volume
- The primary effect of the sympathetic nervous system is to maintain perfusion to the tissues by increasing systemic vascular resistance (SVR)
- The augmented venous tone increases the preload

Mechanisms 5

(anemia due to blood loss)

- In states of hypovolemic hypoxia, the increased venous tone due to sympathetic discharge is thought to dominate the vasodilator effects of hypoxia
- Counterregulatory hormones (e.g., glucagon, epinephrine, cortisol) are thought to shift intracellular water to the intravascular space, perhaps because of the resultant hyperglycemia

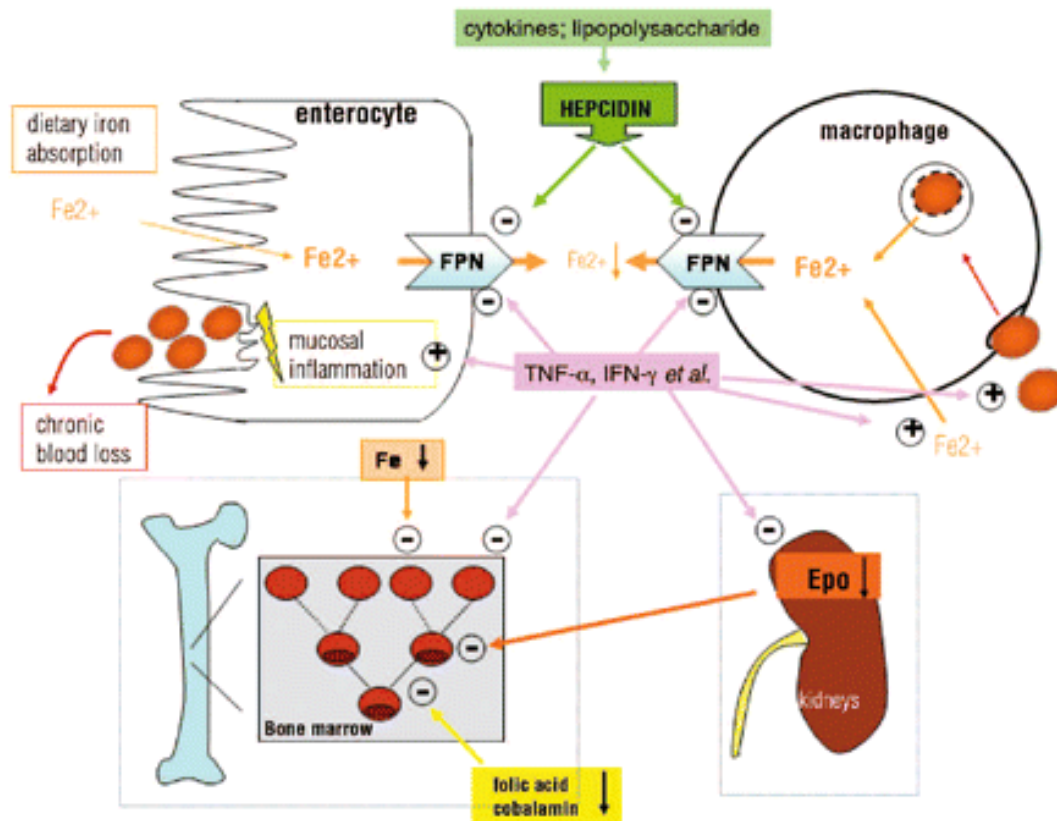
Mechanisms 6a

(anemia due to blood loss)

- Tissue oxygen delivery is the major controlling factor of erythropoiesis through the synthesis and release of erythropoietin (EPO) by the proximal tubular cells or the peritubular interstitial cells in the kidney
- EPO synthesis is governed by the activation of hypoxia inducible factor-1 (HIF-1), which controls the metabolic responses of multiple gene products to hypoxia

Mechanisms 6b

(anemia due to blood loss)



Pathophysiological mechanisms contributing to anemia in patients with Inflammatory Bowel Disease

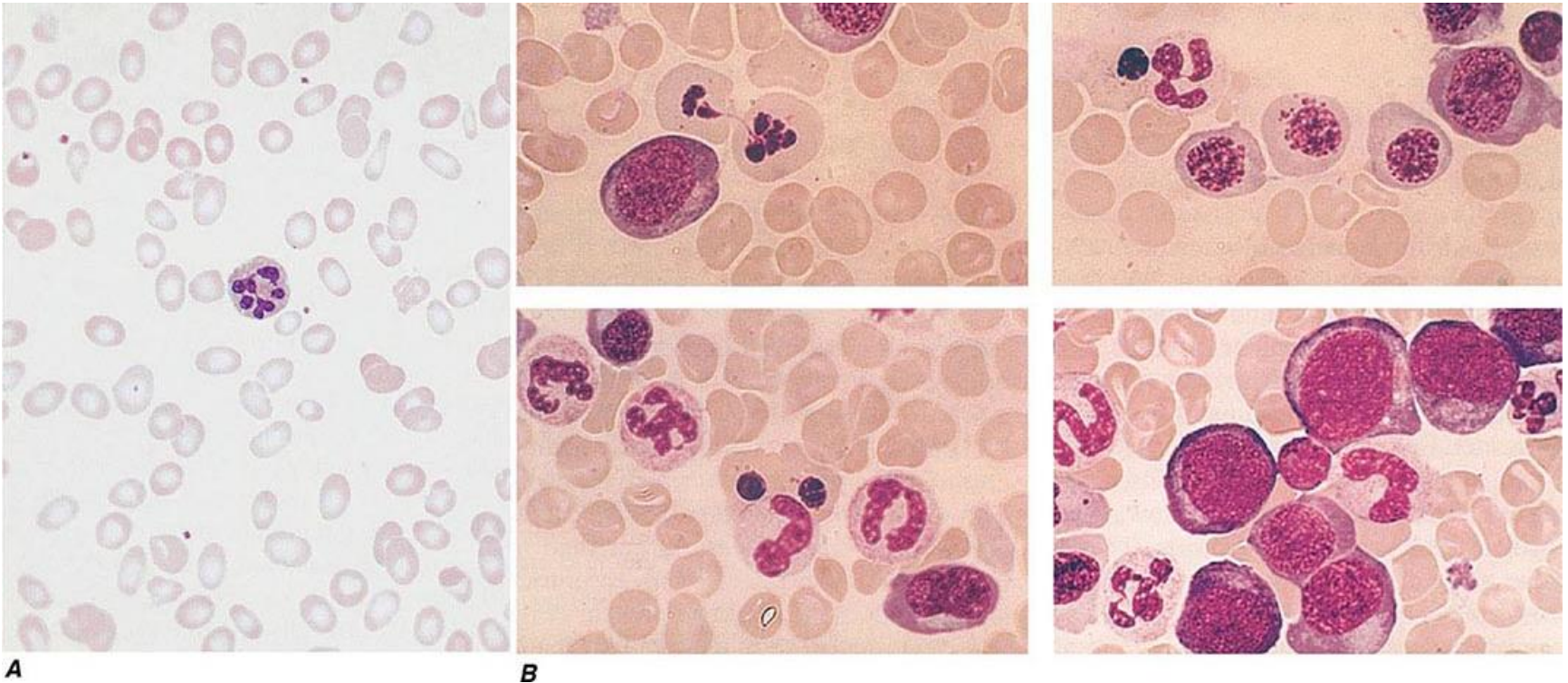
Mechanisms 7a

(anemia due to blood loss)

- HIF-1 binds and activates the hypoxia-responsive transcriptional enhancer in the EPO gene regulatory region that upregulates EPO expression
- EPO stimulates erythroid precursor cells, leading to increased proliferation and shortening of their maturation time
- The marrow responds to increased EPO maximally in 4 to 7 days if enough iron is available

Mechanisms 7b

(anemia due to blood loss)



- A.** The peripheral blood in severe megaloblastic anemia
- B.** The bone marrow in severe megaloblastic anemia

Mechanisms 8

(anemia due to acute blood loss)

- Erythropoiesis can be increased by as much as a factor of 8
- Typical of an endocrine loop feedback mechanism, there is an inverse relation between the hemoglobin and EPO levels measured in the blood
- This relation is somewhat distorted in the anemia associated with inflammation or chronic disease, in which there may be a blunted EPO response

Adaptation to anemia

- Modulation of oxygen affinity—largely mediated by an increase in red blood cell 2,3-biphosphoglycerate
- Increased production of erythropoietin—the main growth factor for red blood cell production
- Redistribution of flow to benefit the myocardium, brain, and muscle
- Increase in cardiac output
- Reduction of mixed venous oxygen tension to increase the arteriovenous oxygen difference

Classification (morphological)

Cell Size	Normal RDW	High RDW
Microcytosis MCV<70 μm^3	Thalassemia minor, anemia of chronic disease, some hemoglobinopathy traits	Iron deficiency, hemoglobin H disease, some anemia of chronic disease, some thalassemia minor, fragmentation hemolysis
Normocytosis: High reticulocyte count Low reticulocyte count	Anemia of chronic disease, hereditary spherocytosis, some hemoglobinopathy traits, acute bleeding	Early or partially treated iron or vitamin deficiency, sickle cell disease
Macrocytosis MCV>100 μm^3	Aplastic anemia, some myelodysplasias	Vitamin B12 or folate deficiency, autoimmune hemolytic anemia, cold agglutinin disease, some myelodysplasias, liver disease, thyroid disease, alcohol

RDW = red cell distribution width; MCV = mean corpuscular volume

Classification

(kinetic: red blood cell loss (bleeding) or destruction (hemolysis))

Acquired

Mechanical (march hemoglobinuria, artificial heart valves)

Microangiopathic (disseminated intravascular hemolysis, thrombotic thrombocytopenic purpura, vasculitis)

Parasites and microorganisms (e.g., malaria, bartonellosis, babesiosis, clostridium perfringens)

Antibody mediated

- Warm-type autoimmune hemolytic anemia
- Cryopathic syndromes (cold agglutinin disease, paroxysmal cold hemoglobinuria, cryoglobulinemia)
- Transfusion reactions

Hypersplenism

Red cell membrane disorders

- Spur cell hemolysis
- Acquired acanthocytosis and acquired stomatocytosis

Chemical injury and complex chemicals (arsenic, copper, chlorate, spider, scorpion, and snake venoms)

Physical injury (heat, oxygen, radiation)

Classification

(kinetic: red blood cell loss (bleeding) or destruction (hemolysis))

Hereditary

Hemoglobinopathies (sickle cell disease, unstable hemoglobins)

Red cell membrane disorders

- Cytoskeletal membrane disorders (hereditary spherocytosis, elliptocytosis, pyropoikilocytosis)
- Lipid membrane disorders (hereditary abetalipoproteinemia, hereditary stomatocytosis)
- Membrane disorders associated with abnormalities of erythrocyte antigens (McLeod syndrome, Rh deficiency Syndromes)
- Membrane disorders associated with abnormal transport (hereditary xerocytosis)

Red cell enzyme defects (pyruvate kinase, 5' nucleotidase, glucose-6-phosphate dehydrogenase deficiencies)

Porphyrias (congenital erythropoietic and hepatoerythropoietic porphyrias, rarely congenital erythropoietic protoporphyria)

Classification

(kinetic: red blood cell underproduction)

Acquired

Pluripotent stem cell failure

- Aplastic anemia (radiation induced, drugs and chemicals, viruses, idiopathic)
- Anemia of leukemia and of myelodysplastic syndromes
- Anemia associated with marrow infiltration (multiple myeloma, myelofibrosis, carcinoma)

Erythroid progenitor cell failure

- Pure red cell aplasia (parvovirus B19 infection, drugs, associated with thymoma, autoantibodies)
- Endocrine disorders (thyroid, adrenal, pituitary hypofunction)
- Acquired sideroblastic anemia (drugs, copper deficiency, etc.)

Functional impairment of erythroid and other progenitors due to nutritional and other causes

- Nutritional deficiencies-iron, vitamin B₁₂, folic acid, pyridoxine
- Chronic renal disease
- Anemia of chronic disease and inflammation

Classification

(kinetic: red blood cell underproduction)

Hereditary

Pluripotent stem cell failure (Fanconi, Shwachman and dyskeratosis congenital syndromes)

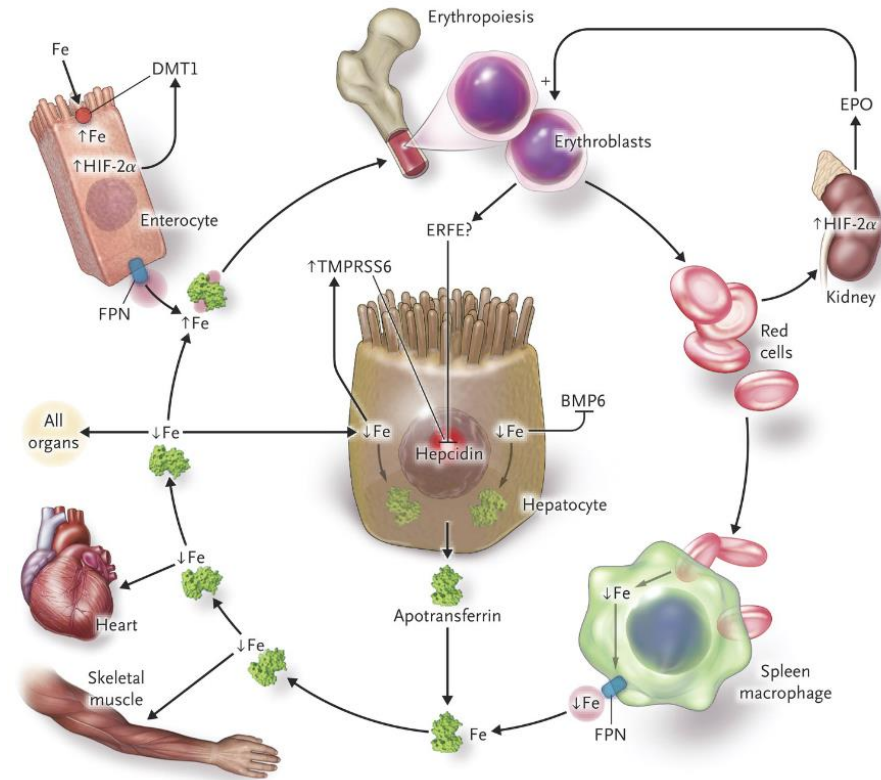
Erythroid progenitor cell failure (Diamond-Blackfan, congenital dyserythropoietic syndromes)

Functional impairment of erythroid and other progenitors due to nutritional and other causes

- Megaloblastic anemias (Imerslund-Gräsbeck disease, intrinsic factor deficiency, transcobalamin II deficiency)
- Inborn purine and pyrimidine metabolic defects (Lesch-Nyhan syndrome, hereditary orotic aciduria)
- Disorders of iron metabolism (atransferrinemia, divalent metal transporter or DMT-1 mutation)
- Hereditary sideroblastic anemia

Classification (clinical)

- Alpha Thalassemia
- Anemia of chronic disease
- Aplastic Anemia
- Beta Thalassemia
- Hemolytic Anemia
- Iron Deficiency Anemia
- Megaloblastic Anemia
- Myelophthisic Anemia
- Pernicious Anemia
- Sickle Cell Anemia
- Spur Cell Anemia



Iron-deficiency anemia is the most common form of anemia in the world

USMLE Step 2 CK` test \2

A 43-year-old woman comes to the physician because of fatigue for 6 months. She has had progressively severe dyspnea on exertion for 6 weeks. She had an extensive abdominal operation 5 years ago for Crohn disease. She does not take any medications. Her temperature is 37°C (98.6°F), pulse is 62/min, respirations are 18/min, and blood pressure is 110/65 mm Hg. Examination of the thyroid gland, lungs, heart, abdomen, and extremities shows no abnormalities. Test of the stool for occult blood is negative. Laboratory studies show:

Hemoglobin 8 g/dL Mean corpuscular volume 70 μm^3
Leukocyte count 9000/mm³ Platelet count 500,000/mm³ .

Which of the following is the most likely diagnosis?: (A) Acute leukemia (B) Anemia of chronic disease (C) Folic acid deficiency (D) Iron deficiency (E) Lyme disease (F) Microangiopathic hemolytic anemia (G) Pernicious anemia (H) Sleep apnea

Clinical investigation

(symptoms)

- Easy fatigue and loss of energy
- Unusually rapid heart beat, particularly with exercise
- Shortness of breath, particularly with exercise
- Pale skin
- Leg cramps
- Coldness in the hands and feet
- Insomnia
- Light-headedness
- Faintness
- Signs of heart failure

Clinical investigation

(symptoms: anemia caused by iron deficiency)

- A hunger for strange substances such as paper, ice, or dirt (a condition called pica)
- Upward curvature of the nails, referred to as koilonychias
- Soreness of the mouth with cracks at the corners



Pica



Koilonychia

Clinical investigation

(symptoms: anemia caused by vitamin B12 deficiency)

- A tingling, "pins and needles" sensation in the hands or feet
- Lost sense of touch
- A wobbly gait and difficulty walking
- Clumsiness and stiffness of the arms and legs
- Dementia



Hand stiffness

Clinical investigation

(symptoms: anemia caused by chronic lead poisoning)

- A blue-black line on the gums referred to as a lead line
- Abdominal pain
- Constipation
- Vomiting

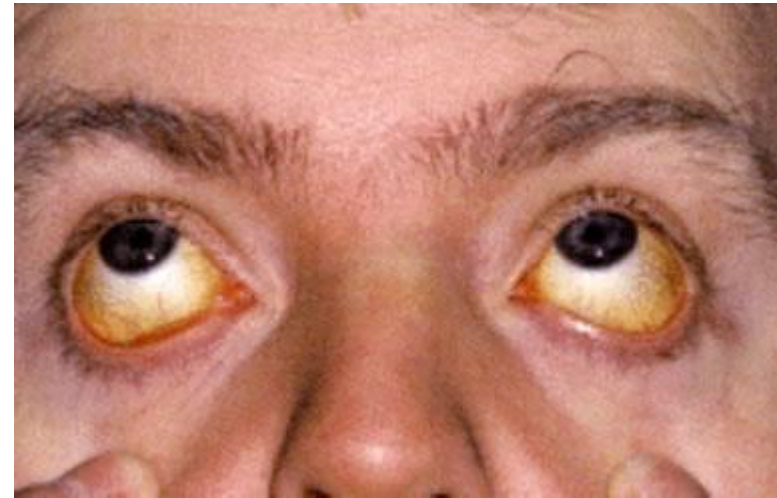


A blue-black line on the gums referred to as a lead line

Clinical investigation

(symptoms: anemia caused by chronic red blood cell destruction)

- Jaundice (yellow skin and eyes)
- Brown or red urine
- Leg ulcers
- Failure to thrive in infancy
- Symptoms of gallstones

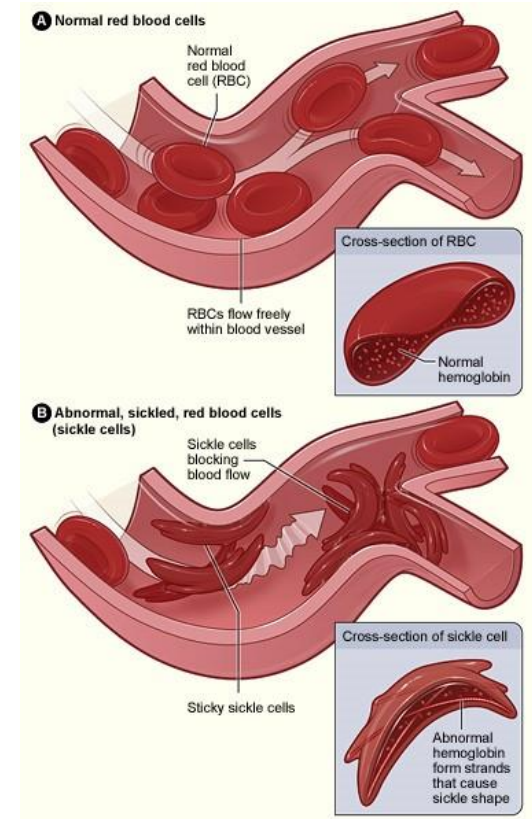


Yellow around eyes
anemia

Clinical investigation

(symptoms: sickle cell anemia)

- Fatigue
- Susceptibility to infection
- Delayed growth and development in children
- Episodes of severe pain, especially in the joints, abdomen, and limbs



Sickle cell anemia

Clinical investigation

(symptoms: anemia caused by sudden red blood cell destruction)

- Abdominal pain
- Brown or red urine
- Jaundice (yellow skin)
- Small bruises under the skin
- Seizures
- Symptoms of kidney failure



The bruise under the skin

USMLE Step 2 CK` test\3

A 15-year-old girl who is a ballet dancer has not had a menstrual period for the past 3 months. Menses were previously regular at 29-day intervals. She has lost weight over the past year; her weight is 70% of that expected for her height. She is afebrile and has purpuric lesions on her extremities and trunk. Platelet, absolute neutrophil, and lymphocyte counts are below the reference range. She has macrocytic anemia. The most likely cause of these symptoms is a deficiency of which of the following nutrients?

(A) Folic acid (B) Iron (C) Linoleic acid (D) Magnesium (E) Niacin (Vitamin PP) (F) Protein (G) Vitamin A (H) Vitamin B6 (pyridoxine) (I) Vitamin C (J) Vitamin D (K) Vitamin E (L) Vitamin K (M) Zinc

Clinical investigation

(accents on history 1)

- The duration of anemia can be established by obtaining a history of previous blood examinations and, if necessary, by acquiring those records
- Similarly, a history of rejection as a blood donor or prior prescription of hematinic provides clues that anemia was detected previously

Clinical investigation

(accents on history 2)

- Obtain a family history for anemia, jaundice, cholelithiasis, splenectomy, bleeding disorders, and abnormal Hbs
- Document the patient's occupation, hobbies, prior medical treatment, drugs (including over-the-counter medications and vitamins), and household exposures to potentially noxious agents (insecticides, paints, solvents, hair dyes)

Clinical investigation

(accents on history 3)

- In searching for blood loss, carefully document pregnancies, abortions, and menstrual loss
- Patients do not appreciate the significance of tarry stools, but changes in bowel habits can be useful in uncovering neoplasms of the colon
- Hemorrhoidal blood loss is difficult to quantify, and it may be overlooked or overestimated from one patient to another

Clinical investigation

(accents on history 4)

- Seek a history of gastrointestinal (GI) complaints that may suggest gastritis, peptic ulcers, hiatal hernias, or diverticula
- Abnormal urine color can occur in renal and hepatic disease and in hemolytic anemia
- A dietary history must include foods that the patient eats and those that he/she avoids, as well as an estimate of their quantity

Clinical investigation

(accents on history 6)

- Changes in body weight are important with regard to dietary intake and can suggest the presence of malabsorption or an underlying wasting disease of infectious, metabolic, or neoplastic origin
- Obtain a history of fever or identify the presence of fever, because infections, neoplasms, and collagen vascular disease can cause anemia

Clinical investigation

(accents on history 7)

- The occurrence of purpura, ecchymoses, and petechiae suggest the occurrence of either thrombocytopenia or other bleeding disorders; this may be an indication either that more than 1 bone marrow lineage is involved or that coagulopathy is a cause of the anemia because of bleeding
- Cold intolerance can be an important symptom of hypothyroidism or lupus erythematosus, paroxysmal cold hemoglobinuria, and certain macroglobulinemias

Clinical investigation

(accents on history 8)

- The relation of dark urine to either physical activity or time of day can be important in march hemoglobinuria and paroxysmal nocturnal hemoglobinuria
- Explore the presence or the absence of symptoms suggesting an underlying disease, such as cardiac, hepatic, and renal disease; chronic infection; endocrinopathy; or malignancy
- A geographic history can also be important in establishing an etiology

Clinical investigation

(accents on physical examination 1a)

- The skin and mucous membranes are often bypassed, so that pallor, abnormal pigmentation, icterus, spider nevi, petechiae, purpura, angiomas, ulcerations, palmar erythema, coarseness of hair, puffiness of the face, thinning of the lateral aspects of the eyebrows, nail defects, and a usually prominent venous pattern on the abdominal wall are missed in the rush to examine the heart and the lungs

Clinical investigation

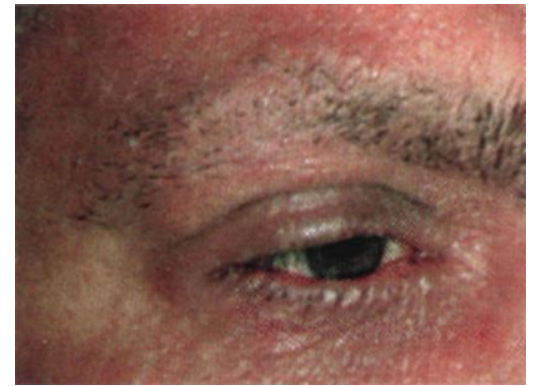
(accents on physical examination 1b)



Purpura



Spider nevi



Thinning of the
lateral aspects of
the eyebrows

Clinical investigation

(accents on physical examination 2)

- Examine optic fundi carefully but not at the expense of the conjunctivae and the sclerae, which can show pallor, icterus, splinter hemorrhages, petechiae, comma signs in the conjunctival vessels, or telangiectasia that can be helpful in planning additional studies
- Perform systematic examination for palpable enlargement of lymph nodes for evidence of infection or neoplasia

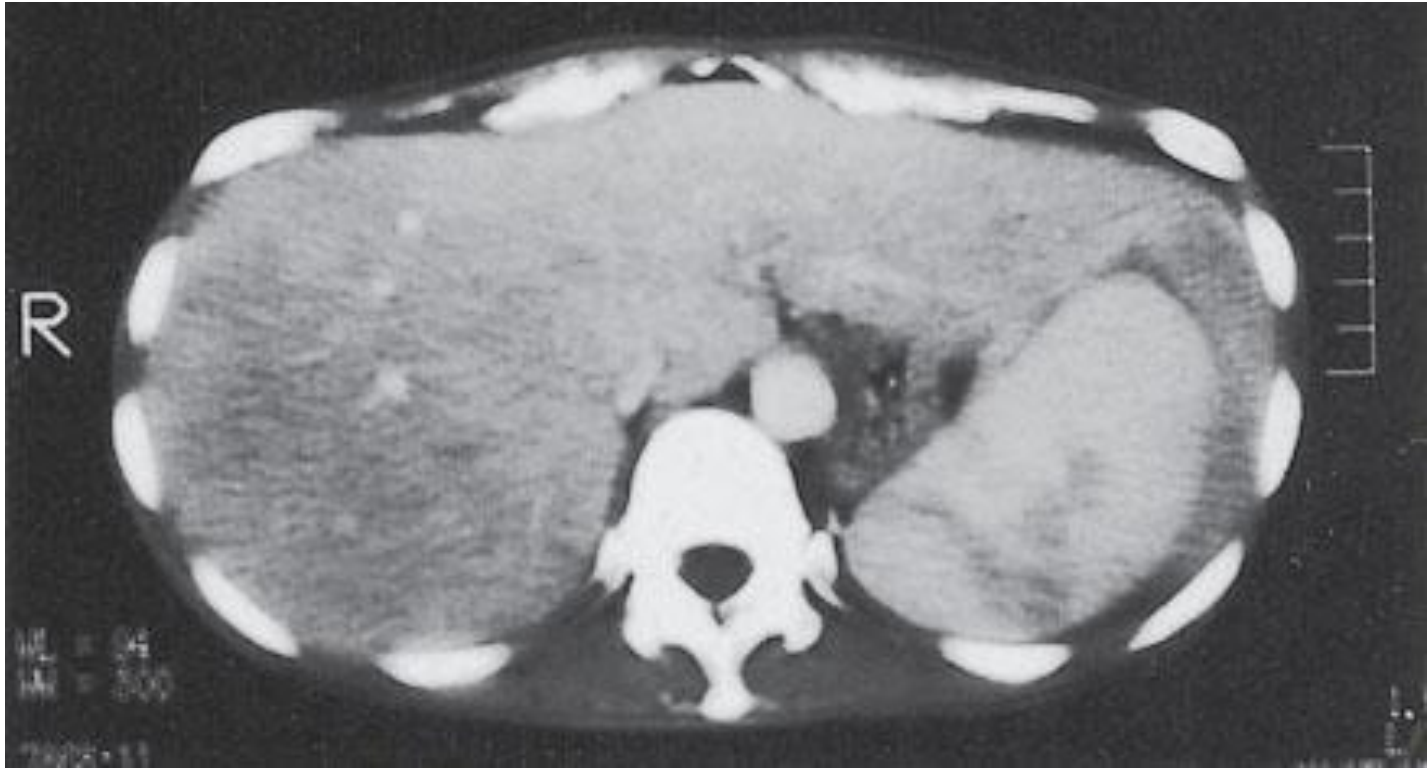
Clinical investigation

(accents on physical examination 3a)

- Bilateral edema is useful in disclosing underlying cardiac, renal, or hepatic disease, whereas unilateral edema may portend lymphatic obstruction due to a malignancy that cannot be observed or palpated
- Carefully search for hepatomegaly and splenomegaly because in patients with chronic disorders, these organs are firm, nontender, and nonnodular, and in patients with carcinoma, they may be hard and nodular

Clinical investigation

(accents on physical examination 3b)



Massive hepatosplenomegaly in a patient with severe malarial anemia due to *Plasmodium falciparum* infection

Clinical investigation

(accents on physical examination 4)

- A rectal and pelvic examination cannot be neglected, because tumor or infection of these organs can be the cause of anemia
- The neurologic examination should include tests of position sense and vibratory sense, examination of the cranial nerves, and testing for tendon reflexes

Clinical investigation

(accents on physical examination 5)

- The heart should not be ignored, because enlargement may provide evidence of the duration and the severity of the anemia, and murmurs may be the first evidence of infective endocarditis that could explain the etiology of the anemia

USMLE Step 2 CK` test \4

A 75-year-old woman has increasing shortness of breath on exertion. Findings on physical examination are unremarkable. X-rays of the chest show no abnormalities of the heart or lungs. Pertinent laboratory findings include: Hematocrit 28% Hemoglobin 9 g/dL Mean corpuscular volume 70 μm^3 Which of the following is the most likely basis for these findings?

- (A) Acquired hemolytic anemia (B) Chronic blood loss
(C) Folic acid deficiency (D) β -Thalassemia minor (E) Pernicious anemia

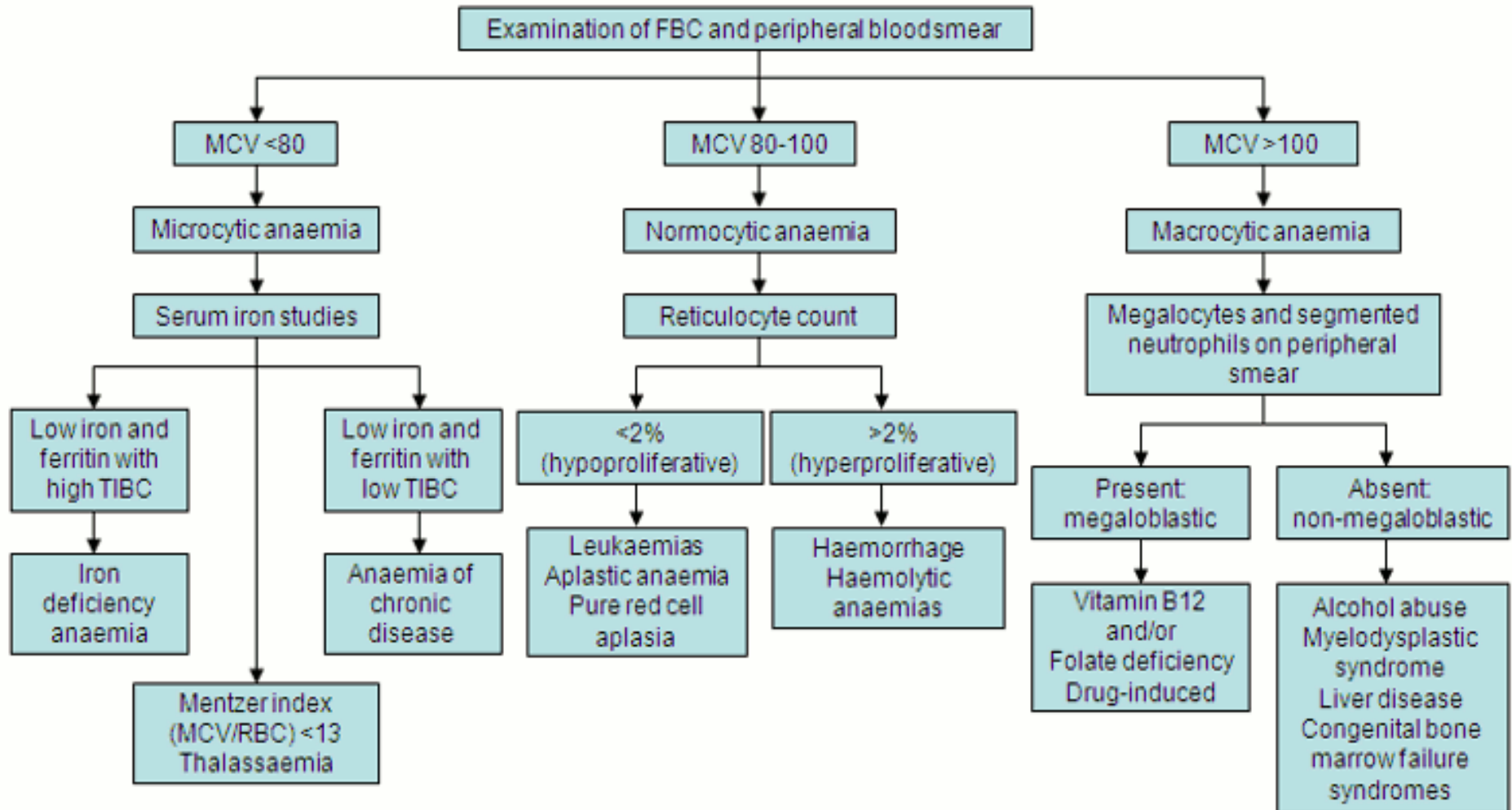
Diagnosis

initial assessment

- Patients may present in several ways
- The urgency with which anemia is evaluated depends on the severity at presentation
- Patients with an acute severe hemorrhage present with hypovolaemia and symptoms and signs of the underlying cause
- Many patients with no acute or active bleeding are asymptomatic, and the anaemia is only noted on a full blood count (FBC) taken as part of the assessment of an unrelated condition
- The first step in diagnosis is to identify the type of anemia that is present, using the results of the FBC

Diagnosis

algorithm for the assessment of anemia



Diagnosis

microcytic anemia: abnormal serum iron studies 1/4

- A low serum iron, a high total iron-binding capacity (TIBC), and a low ferritin indicate iron deficiency anaemia
- Iron deficiency produces an associated reactive thrombocytosis that provides an additional clue
- Iron deficiency is not a diagnosis and requires further investigation to elucidate the cause

Diagnosis

microcytic anemia: abnormal serum iron studies 2/4

- Diets low in meat
- Generalized malabsorption and malnutrition (combined vitamin B12 and/or folate deficiency)
- A history of bleeding (excessive menstrual losses in women, upper and lower GI bleeding, peptic ulcer disease, cirrhosis, idiopathic pulmonary hemosiderosis, excessive blood donation, runner's anaemia, etc.)

USMLE Step 2 CK` test \5

A 54-year-old female with megaloblastic anemia and ataxia is given radiolabeled cobalamin by mouth followed by an intramuscular injection of unlabeled cobalamin. The urine radioactivity level measured afterwards is determined to be normal. Which of the following is the most likely cause of this patient's symptoms?

- ☐ A. Dietary cobalamin deficiency
- ☐ B. Atrophic gastritis
- ☐ C. Nontropical sprue
- ☐ D. Fish tapeworm infestation
- ☐ E. Chronic low-volume GI bleeding

Diagnosis

microcytic anemia: abnormal serum iron studies 3/4

- Signs of iron deficiency (koilonychia, angular cheilosis, glossitis, thinning hair)
- Investigations are guided by the history and examination, and include the fecal occult blood testing, upper GI endoscopy, immunoglobulin A-tissue transglutaminase (IgA-tTG) test (positive in coeliac disease), colonoscopy, flow cytometry (if there is a history of passing red urine), transvaginal ultrasound (causes of menorrhagia)

Diagnosis

microcytic anemia: abnormal serum iron studies 4/4

- A low serum iron, a low total iron-binding capacity, and a low ferritin suggest anaemia of chronic disease
- A history of an underlying inflammation (infection, neoplasms, autoimmune reactions, and injury to tissue from trauma and surgery) is usually present
- A serum erythropoietin level is usually normal or mildly elevated
- Hypothyroidism and vitamin C deficiency may produce a falsely low ferritin level

Diagnosis

microcytic anemia: normal serum iron studies 1/5

- The most important cause to exclude is thalassemia
- A family history is usually present
- The disease is more common in individuals of Mediterranean, Middle Eastern, or Southeast Asian descent
- The severity ranges from asymptomatic to severe transfusion-dependent symptoms

Diagnosis

microcytic anemia: normal serum iron studies 2/5

- The examination findings may be normal, or reveal splenomegaly, jaundice, abdominal distension, and icterus
- Morphological changes including skeletal abnormalities, a large head, chipmunk facies, and misaligned teeth are seen in beta-thalassemia intermedia and major

Diagnosis

microcytic anemia: normal serum iron studies 3/5

- Distinct features on the FBC that suggest the diagnosis include a marked decrease in MCV (usually close to 70 femtolitres [fL]) with a low mean corpuscular Hb, target cells on the peripheral smear, and an elevated reticulocyte count ($>2\%$)
- A Mentzer's index (MCV/RBC) <13 is suggestive of thalassemia, and an index >14 suggests iron deficiency

Diagnosis

microcytic anemia: normal serum iron studies 4/5

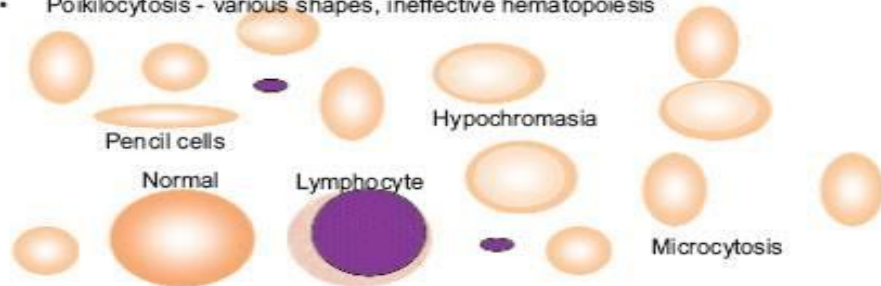
- Thalassemia is diagnosed using Hb electrophoresis
- The presence of Hb H, Hb Bart, and concomitant hemoglobinopathies (Hb E, Hb S, Hb C, Hb D) is diagnostic of alpha-thalassemia
- A high HbF with minimal or absent HbA and an elevated HbA2 is diagnostic of beta-thalassemia

Diagnosis

microcytic anemia: between IDA and Thalassemia 5/5

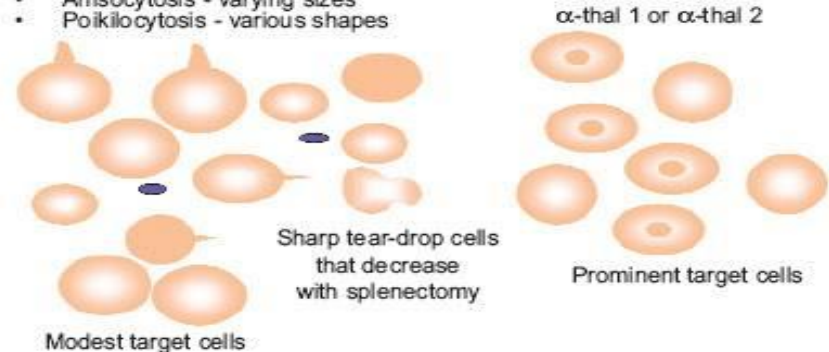
Microcytic Anemia - Iron Deficiency anemia

- Anisocytosis - varying sizes
- Poikilocytosis - various shapes, ineffective hematopoiesis



Microcytic Anemia - Thalassemia - Major

- Anisocytosis - varying sizes
- Poikilocytosis - various shapes



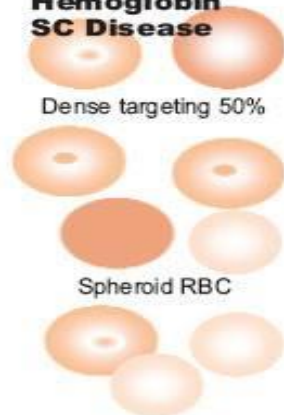
Anemia & Thalassemia: Differential Diagnosis

Differential Features	Iron Deficiency Anemia	Thalassemia
Mentzer's index = MCV/RBC*	> 13	< 13
RDW (red cell distribution width)*	High (wide)	Normal
Iron, ferritin, transferrin saturation**	Low	Normal
TIBC (transferrin)	High	Normal
Other diagnostic tools	Work up the cause of iron deficiency	α-thal (Asian): molecular test; β-thal: electrophoresis

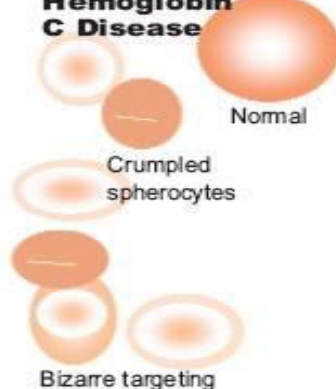
*High sensitivity, low specificity; index values defined in Mentzer WC, Lancet 1973;1:882.

**Higher specificity, MCV, mean corpuscular volume

Hemoglobin SC Disease



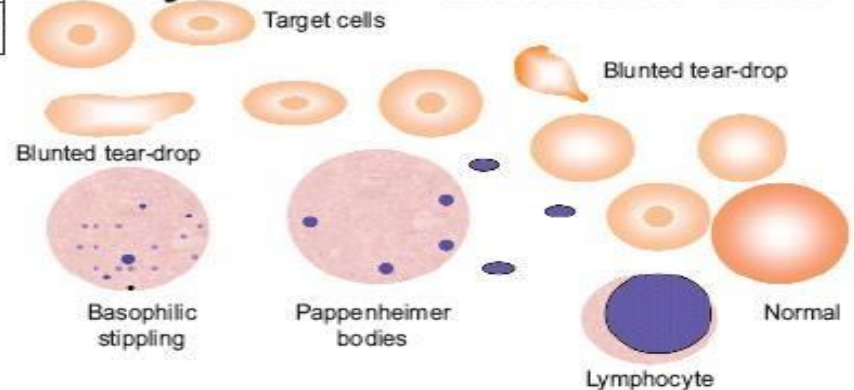
Hemoglobin C Disease



Hemoglobin E Disease



Microcytic Anemia - Thalassemia - Minor



USMLE Step 2 CK` test \6

A 25-year-old woman has a routine, pre-employment physical examination. Laboratory studies include:

Hemoglobin 11.3 g/dL Hematocrit 34% Erythrocyte count 5.2 million/mm³ Mean corpuscular volume 65 μ m³

Follow-up laboratory studies show that the serum iron concentration and iron-binding capacity are within the reference ranges. Hemoglobin electrophoresis shows increased hemoglobin A₂ (5%). Which of the following is the most likely diagnosis?

- (A) Anemia of chronic disease (B) Iron deficiency anemia
(C) Sideroblastic anemia (D) α -Thalassemia minor (E) β -Thalassemia minor

Diagnosis

normocytic anemia: hypoproliferative 1/11

- Normocytic anaemia include disorders that decrease RBC production
- Hematological malignancies and aplastic anaemia are the most important diagnoses to exclude, and are usually associated with multiple cytopenias
- An isolated anemia is usually due to pure red cell aplasia, which may be self-limiting or persistent

Diagnosis

normocytic anemia: hypoproliferative 2/11

- Chronic renal failure or hypothyroidism can cause an isolated anaemia
- Secondary hyperparathyroidism exacerbates the anaemia of chronic renal failure
- Symptoms of bleeding, easy bruising, night sweats, or weight loss suggest hematological malignancy or aplastic anaemia

Diagnosis

normocytic anemia: hypoproliferative 3/11

- Parvovirus infection, infectious mononucleosis, viral hepatitis, malaria, respiratory infections, gastroenteritis, primary atypical pneumonia, and mumps can result in a self-limiting pure red cell aplasia
- Antiepileptic medications (phenytoin, carbamazepine, valproate sodium), azathioprine, sulfonamides, isoniazid, and procainamide cause pure red cell aplasia

Diagnosis

normocytic anemia: hypoproliferative 4/11

- Benzene, penicillamine, and gold can cause aplastic anaemia
- Chloramphenicol can cause either aplastic anaemia or pure red cell aplasia
- Chemotherapy causes pancytopenia.
- Radiotherapy, especially to pelvic or sternal areas, can cause pancytopenia
- A history of immunosuppression or chronic hepatitis suggests persistent pure red cell aplasia

Diagnosis

normocytic anemia: hypoproliferative 5/11

- There may be a history or features of chronic renal failure or hypothyroidism
- Ecchymoses or petechiae due to thrombocytopenia suggest hematological malignancy, myelodysplastic syndrome, or aplastic anaemia
- Lymphadenopathy or fever suggest malignancy or infections (e.g., infectious mononucleosis)

Diagnosis

normocytic anemia: hypoproliferative 6/11

- Splenomegaly may be seen in hematological malignancies
- Clinical features of systemic lupus erythematosus (SLE), rheumatoid arthritis, dermatomyositis, polyarteritis nodosa, or scleroderma resulting in persistent pure red cell aplasia may be present
- Abnormal lung examination (if lung cancer is the primary cancer) or a breast mass (if breast cancer is the primary) may be present

Diagnosis

normocytic anemia: hypoproliferative 7/11

- A positive Trousseau's sign or Chvostek's sign in patients with chronic renal failure indicates hypocalcemia, probably due to associated secondary hyperparathyroidism
- FBC may show an associated cytopenia and characteristic changes specific to a hematological malignancy
- A pancytopenia suggests aplastic anaemia, or may be due to chemotherapy or radiotherapy

Diagnosis

normocytic anemia: hypoproliferative 8/11

- An isolated anemia suggests pure red cell aplasia or anemia due to chronic renal failure
- Bone marrow aspiration provides a definitive diagnosis of aplastic anemia, acute leukemia, chronic myelogenous leukemia (CML), or bone marrow metastases
- Antiparvovirus antibodies are positive in parvovirus infection, the most common infectious cause of pure red cell aplasia

Diagnosis

normocytic anemia: hypoproliferative 9/11

Other tests to consider:

- Hepatitis serology, to exclude an active hepatitis
- Monospot test or Epstein-Barr virus (EBV) IgM, to exclude infectious mononucleosis
- Thick and thin peripheral smear, to exclude malaria if history and findings suggest it
- Thyroid function tests; TSH is elevated and free T4 reduced in hypothyroidism
- Antinuclear antibodies, which are positive in SLE or scleroderma

Diagnosis

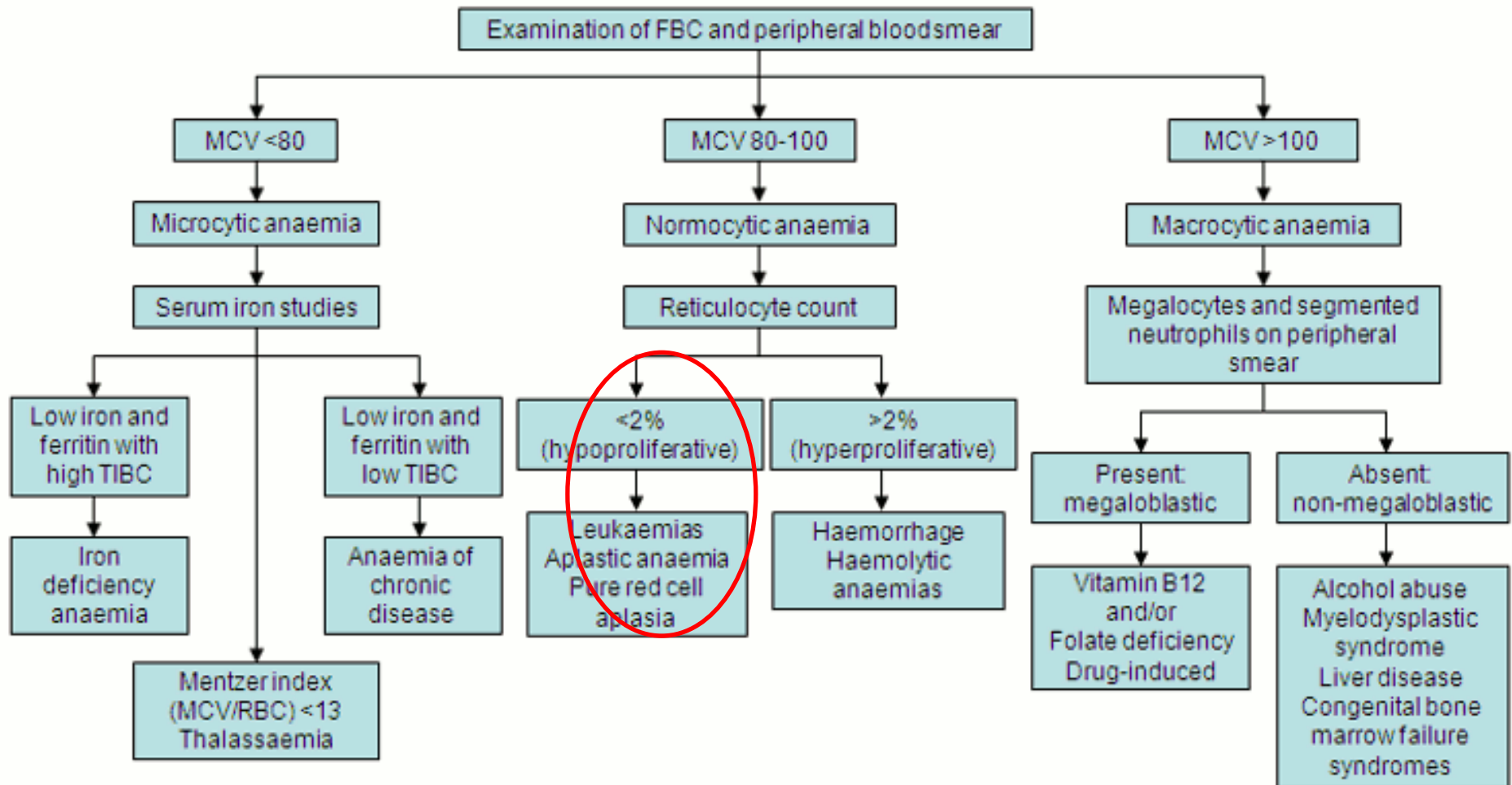
normocytic anemia: hypoproliferative 10/11

Other tests to consider:

- Rheumatoid factor, which is positive in rheumatoid arthritis
- Serum CK, which is elevated in dermatomyositis
- Chest x-ray, which may show infiltrates in atypical pneumonia or a smooth mass in thymoma
- Erythropoietin levels, which may be decreased in patients with chronic renal failure
- Serum calcium and parathyroid hormone levels should be considered if associated secondary hyperparathyroidism is suspected

Diagnosis

normocytic anemia: hypoproliferative 11/11



Diagnosis

normocytic anemia: hyperproliferative 1 /15

- Potential diagnoses include hemolytic anemias (microangiopathic hemolytic anemias, autoimmune hemolytic anemia, drugs, infections, inherited conditions, transfusion reactions, or burns)
- Drugs that can cause hemolysis include penicillin, methyldopa, levodopa, quinidines, cephalosporins, and some NSAIDs

Diagnosis

normocytic anemia: hyperproliferative 2/15

- Cyclosporine, tacrolimus, clopidogrel, oral contraceptive pills, and some chemotherapy drugs may cause hemolytic uremic syndrome
- The triggers of disseminated intravascular coagulation (DIC), that include ongoing severe infection, sepsis, malignancy, obstetric emergency, trauma, burns, envenomation, drug overdose, or any cause of endothelial damage

Diagnosis

normocytic anemia: hyperproliferative 3/15

- The presence of acute-onset neurological symptoms, including headache, confusion, focal weakness, seizures, or coma, should prompt suspicion of thrombotic thrombocytopenic purpura (TTP)
- Female patients may have associated menorrhagia

Diagnosis

normocytic anemia: hyperproliferative 4/15

- Sudden-onset dizziness, headache, mental status changes, loss of sensation or motor strength, chest pain or pressure, dyspnoea, or oedema in a patient with known hypertension should prompt suspicion of malignant hypertension; a history of renal failure or eclampsia may also be present
- An expanding vascular skin lesion in a young infant or child should prompt suspicion of a hemangioma

Diagnosis

normocytic anemia: hyperproliferative 5/15

- A history of prosthetic valve replacement may indicate hemolysis induced by the prosthesis
- Cutaneous burns affecting more than 10% of the body surface area can cause a hemolytic anaemia, or trigger DIC
- Infective causes include cytomegalovirus (CMV), infectious mononucleosis, toxoplasmosis, and leishmaniosis

Diagnosis

normocytic anemia: hyperproliferative 6/15

- Bloody diarrhoea should prompt suspicion of *Escherichia coli* infection and hemolytic uraemic syndrome
- Patients with inherited hemolytic anemias such as sickle cell anaemia, hereditary spherocytosis, or glucose-6-phosphate dehydrogenase (G6PD) deficiency may have a positive family history

Diagnosis

normocytic anemia: hyperproliferative 7/15

- Persistent pain in the skeleton, chest, or abdomen; priapism; lower-extremity skin ulcers; or an acute pneumonia-like syndrome suggest sickle cell anemia
- There may be a previous history of autoimmune disease (e.g., SLE, rheumatoid arthritis, scleroderma) or lymphoproliferative disorders (non-Hodgkin's lymphoma, chronic lymphocytic leukemia), which can lead to autoimmune hemolytic anemia

Diagnosis

normocytic anemia: hyperproliferative 8/15

- The autoimmune diseases may also cause pure red cell aplasia, in which case the reticulocyte count would be low, with normal lactate dehydrogenase, haptoglobin, and bilirubin levels
- Recent blood transfusion may indicate hemolysis due to a transfusion reaction
- Occupational or home exposure to lead should prompt suspicion of lead toxicity

Diagnosis

normocytic anemia: hyperproliferative 9/15

- Features of microangiopathic disease: purpura or ecchymoses, malignant hypertension, edema, oliguria or polyuria, focal neurological signs, and hypertensive retinopathy
- Splenomegaly is seen in hereditary spherocytosis
- Lymphadenopathy may indicate infectious mononucleosis, leukemia, lymphoma, or autoimmune disease

Diagnosis

normocytic anemia: hyperproliferative 10/15

- A thrombocytopenia with schistocytes strongly suggests a microangiopathic hemolytic anemia
- Spherocytes suggest autoimmune hemolytic anaemia or hereditary spherocytosis
- Hereditary spherocytosis is associated with increased mean corpuscular Hb
- Sickling of RBCs is diagnostic of sickle cell anemia

Diagnosis

normocytic anemia: hyperproliferative 11/15

- Heinz bodies, eccentrocytes, or bite cells are seen in G6PD deficiency
- Elevated lactate dehydrogenase and bilirubin levels with a decreased haptoglobin are strongly suggestive of a hemolytic anemia
- Serum creatinine may be elevated in patients with hemolytic uraemic syndrome or malignant hypertension

Diagnosis

normocytic anemia: hyperproliferative 12/15

- Prothrombin time and activated partial prothrombin time, which are prolonged in DIC but normal in other microangiopathic hemolytic anemias
- DIC panel shows elevated D-dimers and fibrin degradation products with low fibrinogen in patients with DIC
- X-rays and MRI scanning of suspected regions reveal internal hemangiomas

Diagnosis

normocytic anemia: hyperproliferative 13/15

- Direct antiglobulin (Coombs') test is positive in autoimmune hemolytic anemia
- Sickle cell anaemia is diagnosed on FBC
- Osmotic fragility test is positive in hereditary spherocytosis
- G6PD assays identify deficiencies of the enzyme

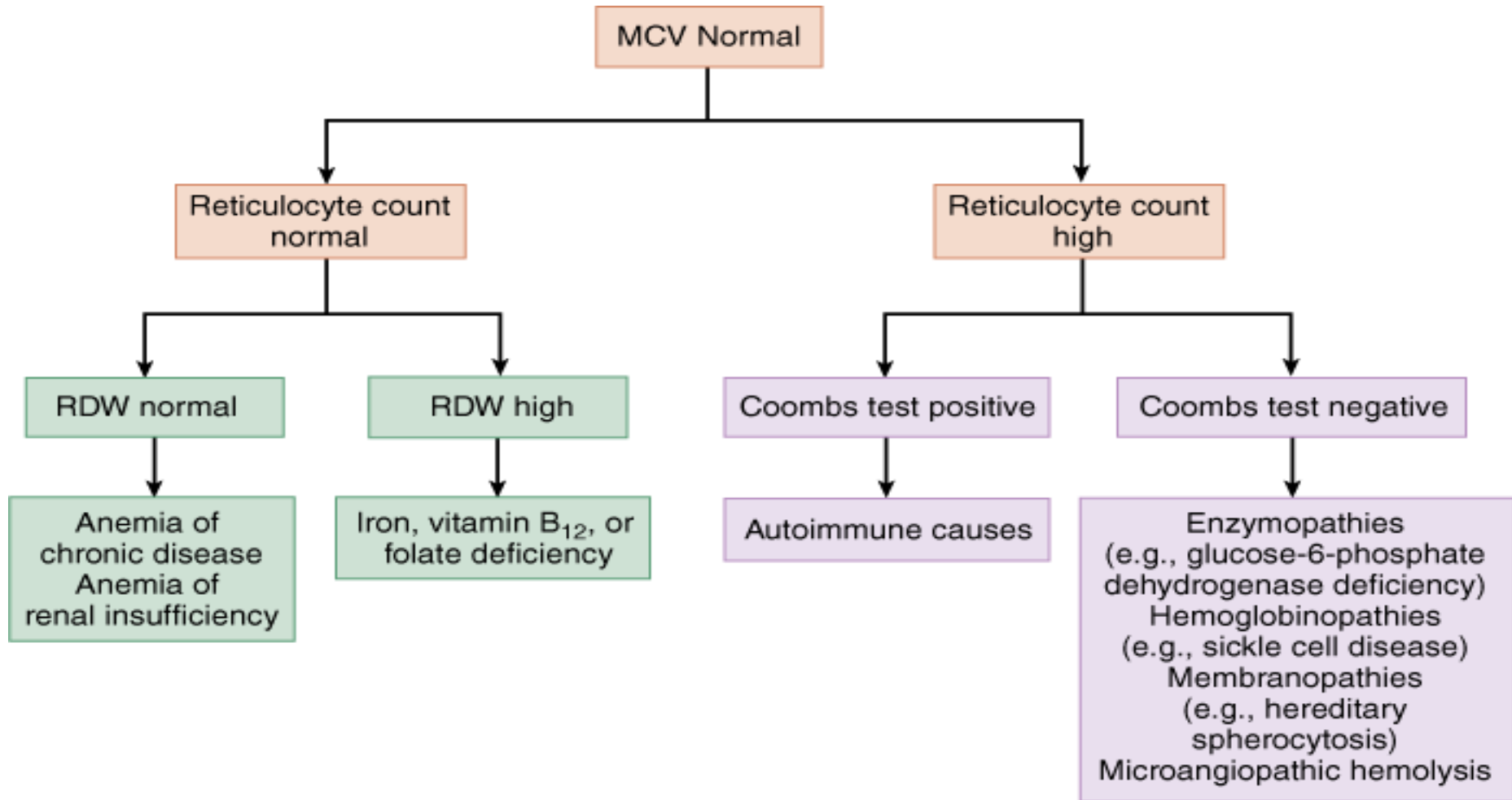
Diagnosis

normocytic anemia: hyperproliferative 14/15

- Monospot test or EBV IgM is positive in infectious mononucleosis
- CMV IgM is positive in CMV infection
- Double-sandwich IgM ELISA or IgG avidity test is positive for IgM in acute toxoplasmosis
- Splenic or bone marrow aspirate shows amastigotes of the parasite in leishmaniosis
- Blood lead levels, which are elevated in lead toxicity

Diagnosis

normocytic anemia: hyperproliferative 15/15



Diagnosis

macrocytic anemia: megaloblastic 1/5

- The main causes to consider are vitamin B12 or folate deficiency, or drugs that interfere with DNA synthesis
- Discontinuation of causative medications leads to resolution of the anaemia
- Poor intake due to malnutrition, alcohol abuse, or strict vegan or low-protein diets can produce deficiency of vitamin B12 and/or folate

Diagnosis

macrocytic anemia: megaloblastic 2/5

- A history of coeliac disease, tropical sprue, Crohn's disease, previous gastric or intestinal surgery, or bacterial overgrowth may indicate malabsorption
- A swollen, red, painful tongue; angular stomatitis; patchy hyperpigmentation of the skin and mucous membranes; and a persistent mild pyrexia are symptoms of folate deficiency

Diagnosis

macrocytic anemia: megaloblastic 3/5

- Known causative medications include purine analogues, pyrimidine analogues, reductase inhibitors, methotrexate, trimethoprim, anticonvulsants, oral contraceptives, cycloserine, p-aminosalicylic acid, metformin, colchicine, neomycin, and biguanides
- Hydroxyurea, in particular, is known to cause oval macrocytosis with MCV >110 femtolitres (fL)

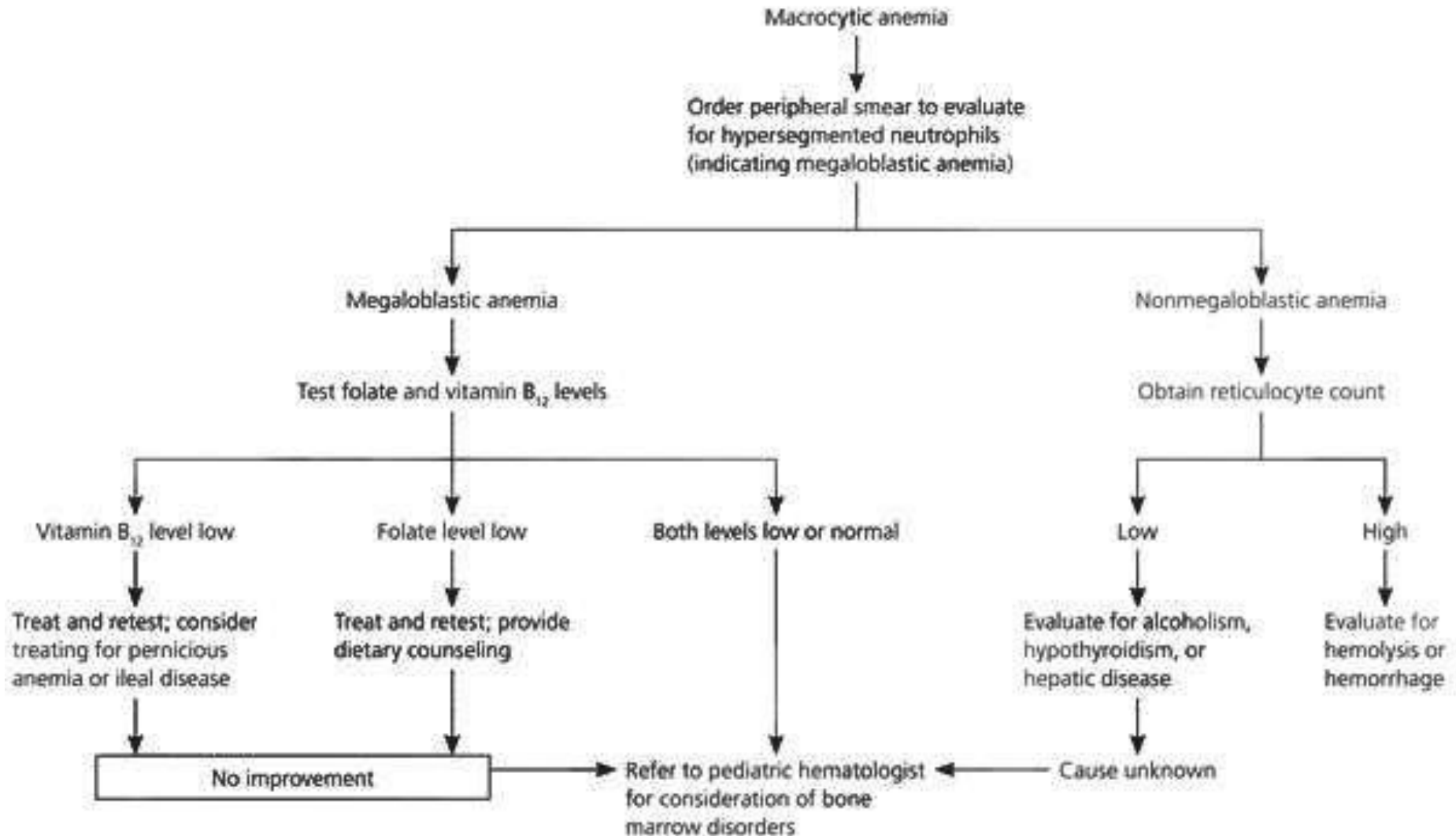
Diagnosis

macrocytic anemia: megaloblastic 4/5

- Serum vitamin B12 levels are decreased and serum methylmalonic acid levels are elevated in vitamin B12 deficiency
- Normal serum homocysteine levels make folate deficiency unlikely
- Anti-intrinsic factor and parietal cell antibodies are positive in pernicious anemia

Diagnosis

macrocytic anemia: megaloblastic 5/5



USMLE Step 2 CK test \7

A 34-year-old male who recently emigrated from Asia comes to the clinic and complains of a two-month history of exertional shortness of breath and easy fatigability. He has been taking isoniazid and rifampin for his tuberculosis, which was diagnosed four months ago. Due to his religious beliefs, he completely turned into a vegetarian for the last year. Physical examination reveals severe pallor. Peripheral smear shows macrocytosis with hypersegmented polymorphonuclear neutrophils. His WBC and platelet counts are within normal limits. This patient's most likely problem is due to which of the following?

- ☐ A. B12 deficiency because of the vegetarian diet
- ☐ B. B12 deficiency because of the pernicious anemia
- ☐ C. Drug-induced B12 deficiency
- ☐ D. Myelodysplastic syndrome
- ☐ E. Chronic myeloid leukemia

Diagnosis

macrocytic anemia: non-megaloblastic 1/6

- Causes to consider non-megaloblastic macrocytic anemia include alcohol abuse, myelodysplastic syndrome, chronic liver disease, and congenital bone marrow failure
- High alcohol intake indicates alcohol-induced anemia, which usually persists for months after total abstinence
- A history of chronic liver disease indicates liver disease-induced anaemia

Diagnosis

macrocytic anemia: non-megaloblastic 2/6

- History of prior exposure to petroleum distillates (especially benzene), chemotherapy, or radiotherapy should prompt suspicion of myelodysplastic syndrome
- A history of fever, chills, fatigue, weakness, recurrent infection, anorexia, night sweats, shortness of breath, and easy bruising should prompt suspicion of myelodysplastic syndrome

Diagnosis

macrocytic anemia: non-megaloblastic 3/6

- Recurrent infections in an infant should prompt suspicion of congenital bone marrow failure syndromes
- Examination may reveal stigmata of chronic alcoholism or chronic liver disease
- Dyskeratosis congenital is characterised by the triad of abnormal nails, reticulated skin rash, and leukoplakia

Diagnosis

macrocytic anemia: non-megaloblastic 4/6

- Skeletal abnormalities and growth retardation are seen in Shwachman-Diamond syndrome
- FBC shows associated neutropenia and thrombocytopenia with macro-ovalocytes in myelodysplastic syndrome
- Bone marrow aspiration and biopsy shows myeloblasts with immature precursors in myelodysplastic syndrome

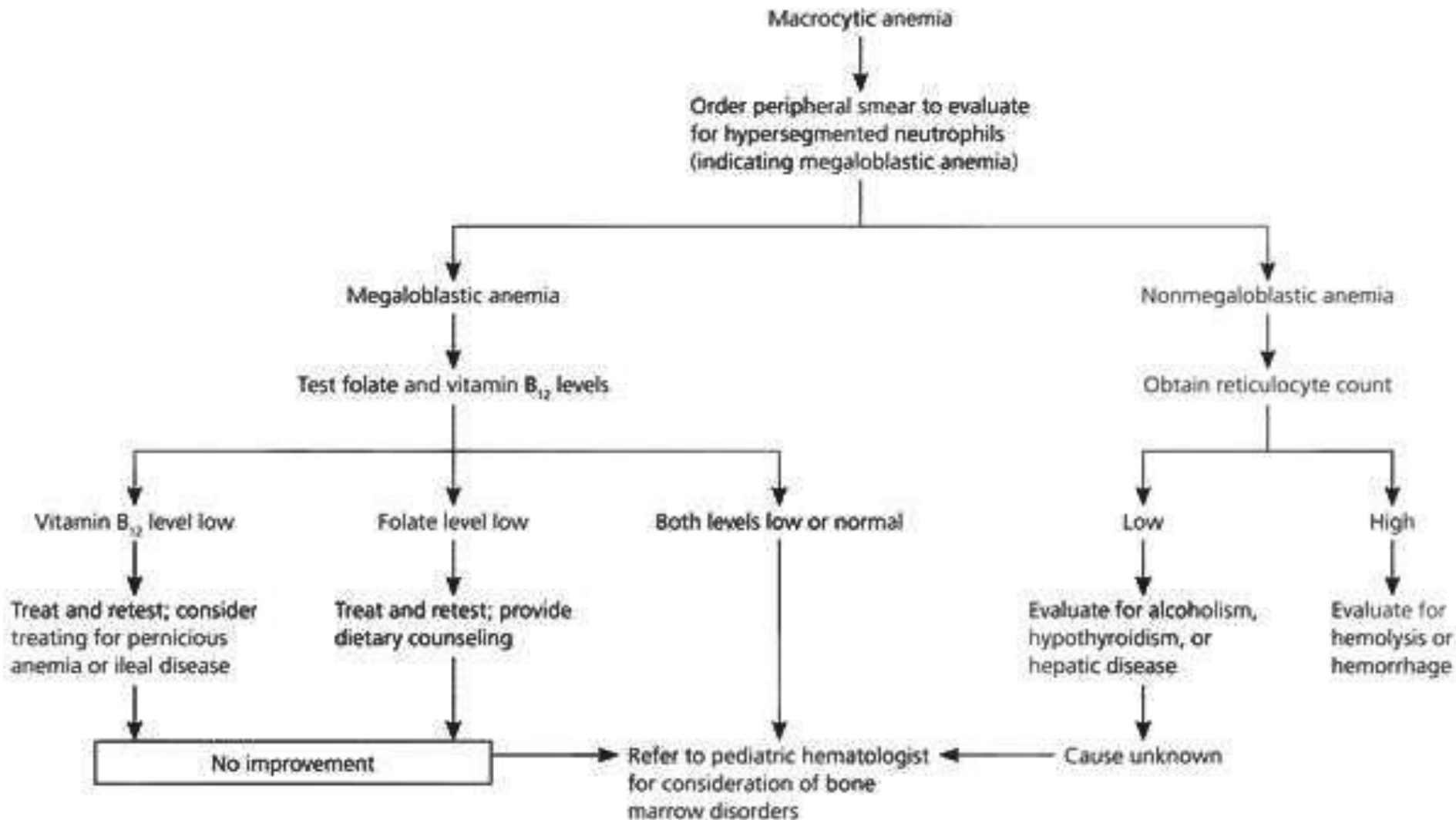
Diagnosis

macrocytic anemia: non-megaloblastic 5/6

- Diagnostic features of congenital bone marrow failure syndromes are also identified
- Cytogenetics reveal chromosomal translocations in myelodysplastic syndrome
- Additional tests for congenital bone marrow syndromes: diepoxybutane or mitomycin-c fragility test is positive in Fanconi anaemia
- Genetic testing reveals underlying mutations

Diagnosis

macrocytic anemia: megaloblastic 6/6



USMLE Step 2 CK` test\8

An 80-year-old female is brought to your office, by her son, because of severe fatigue. She lives alone and is suffering from severe degenerative joint disease, which puts her in a house arrest-type state. Her son usually helps with getting grocery. Her only other medical problem is hypertension. She takes hydrochlorothiazide and acetaminophen. Her vitals are stable. On examination, she has pallor, and evidence of severe degenerative joint disease. Which of the following is the most likely cause of pallor in this patient?

- ☐ A. Vitamin D deficiency
- ☐ B. Vitamin C deficiency
- ☐ C. Iron deficiency
- ☐ D. Folate deficiency
- ☐ E. Chronic hemolysis
- ☐ F. Anemia of chronic disease
- ☐ G. Vitamin B12 deficiency
- ☐ H. Copper deficiency

Treatment

patient education

- Inform patients of the etiology of their anemia, the significance of their medical condition, and the therapeutic options available for treatment
- If no effective specific treatment of the underlying disease exists, educate patients requiring periodic transfusions about the symptoms that herald the need for transfusion
- Likewise, they should be aware of the potential complications of transfusion

Treatment

iron deficiency anemia

- Iron deficiency anemia is treated with changes in diet and iron supplements
- If the underlying cause of iron deficiency is loss of blood — other than from menstruation — the source of the bleeding must be located and stopped

Treatment

vitamin deficiency anemias

- Folic acid and vitamin C deficiency anemias are treated with dietary supplements and increasing these nutrients in diet
- If patient's digestive system has trouble absorbing vitamin B-12 from the food, he may receive vitamin B-12 injections

Treatment

anemia of chronic disease

- There's no specific treatment for anemia of chronic disease
- If symptoms become severe, a blood transfusion or injections of synthetic erythropoietin, a hormone normally produced by your kidneys, may help stimulate red blood cell production and ease fatigue

Treatment

aplastic anemia

- Treatment for aplastic anemia may include blood transfusions to boost levels of red blood cells
- Patient may need a bone marrow transplantation if bone marrow can't make healthy blood cells

Treatment

anemias associated with bone marrow disease

Treatment of anemias associated with bone marrow disease can include simple medication, chemotherapy or bone marrow transplantation

Treatment

hemolytic anemias

Managing hemolytic anemias includes avoiding suspect medications, treating related infections and taking drugs that suppress immune system, which may be attacking your red blood cells

Depending on the severity of anemia, a blood transfusion or plasmapheresis may be necessary

Plasmapheresis is a type of blood-filtering procedure
In certain cases, removal of the spleen can be helpful

Treatment

sickle cell anemia

- Treatment for sickle cell anemia may include the administration of oxygen, pain-relieving drugs, oral and intravenous fluids, blood transfusions, folic acid supplements and antibiotics
- A bone marrow transplant may be an effective treatment in some circumstances
- A cancer drug called hydroxyurea (Droxia, Hydrea) also is used to treat sickle cell anemia

Treatment thalassemia

- Thalassemia may be treated with blood transfusions, folic acid supplements, removal of the spleen (splenectomy), a bone marrow transplant or a another drug

Treatment

erythropoiesis-stimulating agent

- The motive for the administration of an erythropoiesis-stimulating agent (ESA) is to maintain hemoglobin at the lowest level that both minimizes transfusions and meets the individual persons needs
- They should not be used for mild or moderate anemia and are not recommended in people with chronic kidney disease unless hemoglobin levels are less than 10 g/dL or they have symptoms of anemia
- Their use should be along with parenteral iron

Treatment

oral iron

- Mild to moderate iron-deficiency anemia is treated by oral iron supplementation with ferrous sulfate, ferrous fumarate, or ferrous gluconate
- When taking iron supplements, stomach upset and/or darkening of the feces are commonly experienced
- The stomach upset can be alleviated by taking the iron with food; however, this decreases the amount of iron absorbed.
- Vitamin C aids in the body's ability to absorb iron, so taking oral iron supplements with orange juice is of benefit

Treatment

oral iron

ORAL IRON THERAPY

- Oral iron treatment may require 3-6 months to replenish body stores.

TABLE SHOWING SOME COMMON ORAL IRON MEDICATION.

Preparation	Tablet size	Elemental iron per tablet	Usual Adult Dosage(per tab)
Ferrous sulfate- hydrated	325mg	65mg	3 to 4
ferrous sulfate- desiccated	200mg	65mg	3 to 4
Ferrous gluconate	325mg	36mg	3 to 4
Ferrous fumarate	100mg	33mg	6 to 8
	325mg	106mg	2 to 3

Treatment

injectable iron

- In cases where oral iron has either proven ineffective, would be too slow (for example, pre-operatively) or where absorption is impeded (for example in cases of inflammation), parenteral iron can be used
- The body can absorb up to 6 mg of iron daily from the gastrointestinal tract
- In many cases the patient has a deficit of over 1,000 mg of iron which would require several months to replace
- This can be given concurrently with erythropoietin to ensure sufficient iron for increased rate of erythropoiesis

Treatment

injectable iron

Iron Product	Iron-Repletion Dose in Patients on Chronic Hemodialysis	Iron-Repletion Dose in Patients Not on Hemodialysis
Iron dextran	100-mg IV q dialysis treatment \times 10 doses	100-mg IV or IM daily \times 10 doses 250-1,000-mg slow IV infusion ^a
Iron sucrose	100-mg IV q dialysis \times 10 doses 200-mg IV q dialysis treatment \times 5 doses	200-mg IV on 5 different occasions in 14 days 500-mg slow IV infusion on Day 1 and Day 14 300-mg, 300-mg, 400-mg IV infusion each 14 days apart
Sodium ferric gluconate	125-mg IV q dialysis treatment \times 8 doses	250-mg slow IV infusion ^a
Ferumoxytol	510-mg IV \times 2 doses 3 to 8 days apart	510-mg IV \times 2 doses 3 to 8 days apart

^a Not FDA approved. IM: intramuscular.
Source: References 11-17.

Treatment

blood transfusions

- Blood transfusions in those without symptoms is not recommended until the hemoglobin is below 60 to 80 g/L (6 to 8 g/dL)
- In those with coronary artery disease who are not actively bleeding transfusions are only recommended when the hemoglobin is below 70 to 80g/L (7 to 8 g/dL)
- Transfusing earlier does not improve survival
- Transfusions otherwise should only be undertaken in cases of cardiovascular instability

Treatment blood transfusions



Treatment

erythropoiesis-stimulating agent



Recombinant human erythropoietin injections

Treatment

hyperbaric oxygen

- Treatment of exceptional blood loss (anemia) is recognized as an indication for hyperbaric oxygen (HBO) by the Undersea and Hyperbaric Medical Society
- The use of HBO is indicated when oxygen delivery to tissue is not sufficient in patients who cannot be given blood transfusions for medical or religious reasons
- HBO may be used for medical reasons when threat of blood product incompatibility or concern for transmissible disease are factors

Treatment hyperbaric oxygen



Prognosis

- The prognosis depends on the underlying cause of the anemia
- The severity of the anemia, its etiology, and the rapidity with which it develops can each play a significant role in the prognosis
- Similarly, the age of the patient and the existence of other comorbid conditions influence outcome

Prophylaxis

- Many types of anemia can't be prevented
- Iron deficiency anemia and vitamin deficiency anemias can be prevented by a diet that includes:
 - Iron (meats, beans, lentils, iron-fortified cereals, dark green leafy vegetables, and dried fruit)
 - Folate (citrus fruits and juices, bananas, dark green leafy vegetables, legumes, and fortified breads, cereals and pasta)
 - Vitamin B-12 (meat and dairy products)
 - Vitamin C (citrus fruits, melons and berries)

Abbreviations

- ADH - antidiuretic hormone
- EPO - erythropoietin
- FBC - full blood count
- GI - gastrointestinal
- Hct - hematocrit
- HIF-1 - hypoxia inducible factor-1
- IVF - intravenous fluid
- MCV - mean corpuscular volume
- NSAID - non-steroidal anti-inflammatory drug
- TBV - total blood volume

Diagnostic guidelines

- [Anaemia management in people with chronic kidney disease\(external link\)](#)
- [Clinical practice guidelines for evaluation of anemia\(external link\)](#)
- [Guidelines for the diagnosis and management of adult aplastic anaemia\(external link\)](#)
- [Guideline for the laboratory diagnosis of functional iron deficiency\(external link\)](#)
- [British consensus guidelines on intravenous fluid therapy for adult surgical patients \(GIFTASUP\)\(external link\)](#)
- [Guidelines for the management of iron deficiency anaemia\(external link\)](#)
- [Significant haemoglobinopathies: guidelines for screening and diagnosis\(external link\)](#)