Anemia

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Background and Introduction

Anemia is a reduction in blood hemoglobin (Hgb) concentration or hematocrit (Hct). Normal values of Hgb and Hct vary based on age, gender, ethnicity, and other special considerations and have been widely studied over the years. Recent data from large samples selected to represent the population of the USA suggests that the lower limit of normal hemoglobin concentrations be 13.7 g/dL in young white men (ages 20–59 years) and 12.9 g/dL in young black men, 13.2 g/dL in white and 12.7 g/dL in black men ages 60 years and over, and 12.2 g/dL in white women and 11.5 g/dL in black women 20 years and over, including elderly women [1]. The lower limit of normal for children age 1–3 years is 11 g/dL, with the cutoff rising to approach adult values by age 15–19 years.

It can be particularly difficult to diagnose the cause of anemia in the elderly population, and between 30 % and 50 % of anemia in this age group can be considered "undiagnosed anemia of the elderly" after extensive workup [2]. People residing at higher altitudes have higher baseline Hgb and Hct levels than residents at sea level. Smokers and patients exposed to significant secondhand smoke may have higher Hgb and Hct levels as well [3]. Endurance athletes can have a "sports anemia" as a result of increased plasma volume that lowers hematocrit despite stimulated erythropoiesis and higher red blood cells counts (RBCs) compared to sedentary individuals [4]. Gastrointestinal (GI) bleeds, anemia of

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chronic inflammation (ACI) due to increased cytokine release with exercise, hemolysis of senescent RBCs in contracting or compressed muscles, hematuria, and sweating can further contribute to this "sports anemia," especially in long-distance runners [4, 5]. Additionally, it is always important to evaluate results in the context of previous data. For example, a low "normal" Hgb may be significant if a recent value was higher.

On occasion, the Hgb and Hct may not accurately reflect red cell mass as they are concentrations and depend on the plasma volume. For example, patients with expanded plasma volume, as in pregnancy or congestive heart failure, may have falsely low values, while patients with plasma contraction, as in burns or dehydration, may have falsely elevated values. In the setting of acute blood loss, both RBCs and plasma are lost equally, and the true degree of anemia may not be appreciated until plasma volume has time to expand.

Anemia may be categorized by the RBC size (microcytic, normocytic, or macrocytic) or by cause (RBC underproduction, RBC destruction, or RBC loss). A patient's history, physical exam, and laboratory studies are integral to determine the etiology of the anemia regardless of the diagnostic approach taken.

Clinical Presentation

Symptoms

Symptoms of anemia are highly variable and depend on the degree of anemia and the rapidity of its development. They arise from the effects of decreased oxygen delivery to end organs and can be exacerbated by hypovolemia. In response to a decrease in Hct, the body increases oxygen extraction by its tissues as well as increases the delivery of oxygen to these tissues by augmenting cardiac output with a faster heart rate and larger stroke volume. Those with mild or gradually developing anemias may be seemingly asymptomatic, although these patients may also demonstrate symptoms that are not yet recognized by the patient and/or physician [6]. Others may present with a range of symptoms including fatigue, weakness, decreased exercise tolerance, dizziness, headache, tinnitus, palpitations, syncope, impaired concentration, and restless leg syndrome (RLS). Some patients experience abdominal discomfort, nausea, and bowel irregularity as blood is shunted from the splanchnic bed. Decreased blood flow to the skin may result in cold intolerance. Patients with preexisting vascular disease are prone to exacerbations of angina, claudication, or cerebral ischemia.

History

Historical clues assist in determining the cause of anemia. Family history of anemia or onset of anemia in childhood suggests an inherited etiology. Chronic medical conditions such as hepatic, renal, endocrine, or inflammatory disorders can lead to anemia of chronic disease (ACD). Malignancies and infections may also cause anemia. Exposure to some medications, alcohol, and toxins (e.g., lead) can lead to anemia due to bone marrow suppression or interference with vitamin absorption. Chronic diarrhea or a history of GI conditions associated with malabsorption suggests a nutritional deficiency anemia. Obesity or a history of bariatric surgery or other GI surgeries can predispose to iron deficiency anemia (IDA). Dietary intake of iron, folate, and vitamin B12 (cobalamin) should be obtained. Paresthesias of the extremities or alteration in mental status may point to vitamin B12 deficiency. A history of gallstones or jaundice points to hemolysis. Pica, especially of ice, suggests iron deficiency. Potential blood loss from the GI tract or heavy uterine bleeding must be ascertained. Frequent blood donations or blood draws in hospitalized patients may lead to an induced anemia.

Physical Examination

Tachycardia and wide pulse pressure may be present in the anemic patient as a result of increased cardiac output. The skin and conjunctiva may demonstrate pallor. In very severe anemias, retinal

hemorrhages may be seen. Jaundice may suggest hemolysis or liver disease. Glossitis can be present in vitamin B12 and iron deficiency. Lymphadenopathy may occur in the presence of hematologic malignancies and infections such as HIV and tuberculosis. A systolic ejection murmur and venous hum may be heard. Signs of liver disease and splenomegaly should be sought. The stool should be examined for blood. Proprioception and balance deficits may occur in vitamin B12 deficiency.

Laboratory Data

Complete Blood Count. Once a patient is determined to be anemic by Hgb and/or Hct, a complete blood count (CBC) with differential should be obtained for the RBC indices as well as the platelet and white blood cell (WBC) values. Mean corpuscular volume (MCV) reflects the size of the RBC. The normal MCV for adults is debatable, with the lower limit of normal defined as 80–82 fl. and the upper limit of normal as 98–100 fl. MCV in children is lower, starting at 70 fl. at 1 year of age and increasing 1 fl/year until adult values are reached at puberty. Table 1 divides common causes of anemia into microcytic (<82 fl), normocytic (82–98 fl), and macrocytic (>98 fl).

The red cell distribution width (RDW) quantitates the variation in size of the RBCs. Normal RDW is less than 14.5 %. An elevation of the RDW may make the MCV by itself less reliable. An example is a patient who has both iron and B12 deficiencies. In this case, the MCV may be normocytic, but the RDW will be elevated [7]. Recent data from ICU and cardiac patients suggests a possible correlation between increased RDW and increased inflammation, oxidant damage, or vascular trauma that may be predictive of poor outcomes irrespective of the presence of anemia [8].

Mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) generally mirror the MCV (i.e., smaller RBCs tend to have lower MCHs and MCHCs, such as in iron deficiency and thalassemias). Larger RBCs tend to have greater MCH and MCHC values, such as in spherocytosis or sickle-cell anemia.

The presence of hypochromic and hyperchromic RBCs is also important in

Table 1 Classification of anemia based on MCV

Microcytic	**Macrocytic**
Iron deficiency	Non-megaloblastic
Thalassemia	Alcoholism
Anemia of chronic disease[a]	Chronic liver disease
Hemoglobin E[a]	Bone marrow disorders
Sideroblastic anemia[a]	Hypothyroidism[a]
Lead poisoning[a]	Sideroblastic anemias[a]
Hereditary[a]	Marked reticulocytosis
Myelodysplastic syndrome[a]	Spurious[a]
Severe alcoholism[a]	Normal variant[a]
Medications[a]	Neonatal period
Normocytic	Megaloblastic
Elevated reticulocyte count	Folate deficiency
Acute blood loss	Poor intake
Hemolysis	Malabsorption
Decreased reticulocyte count	Ethanol
Anemia of chronic disease	Medications
Chronic kidney disease	Pregnancy
Chronic liver failure	Infancy
Endocrine disease	High folate requirement
Iron deficiency	B12 (cobalamin) deficiency
Myelodysplastic syndromes	Pernicious anemia
Aplastic anemia[a]	Gastric or ileal surgery[a]
Pure red cell aplasia[a]	Ileal disease[a]
Myelophthisic anemia[a]	Strict veganism[a]
Sideroblastic anemia[a]	Fish tapeworm infection[a]
	Bacterial overgrowth[a]
	Pancreatic insufficiency[a]
	Medications[a]
	Congenital disorders[a]
	Medications (anticonvulsants, chemotherapy, zidovudine)

[a]Less common

evaluating anemia. Hypochromic erythrocytes (MCHC <28 g/dL) tend to be more prevalent in IDA than in thalassemias, while hyperchromic erythrocytes (MCHC >41 g/dL) can easily identify hereditary spherocytosis [8].

Platelet and WBC counts should be noted. Among other things, decreased platelet levels (thrombocytopenia) and/or decreased WBCs (leukopenia) suggest bone marrow suppression, aplastic anemia, hypersplenism, vitamin B12 deficiencies, infections, or malignancies. Elevated platelet counts (thrombocytosis) are often seen in IDA, trauma, and infections. Increased WBC counts (leukocytosis) can also be seen in infections and malignancies. Severe pancytopenia should prompt a workup for aplastic anemia, hematologic malignancy, or chemotherapy and/or radiation side effects, among other causes.

Reticulocyte Count. Reticulocytes, which are newly formed RBCs, normally account for about 1 % of circulating RBCs. Reticulocyte formation is increased in a normal individual who loses blood, with the degree of reticulocytosis increasing as anemia becomes more severe. Therefore, a patient's reported reticulocyte percentage should be adjusted for the degree of anemia to determine if the bone marrow response is appropriate:

$$\text{corrected reticulocyte \%} = \text{reticulocyte \%} \times \text{patient's Hct/normal Hct.}$$

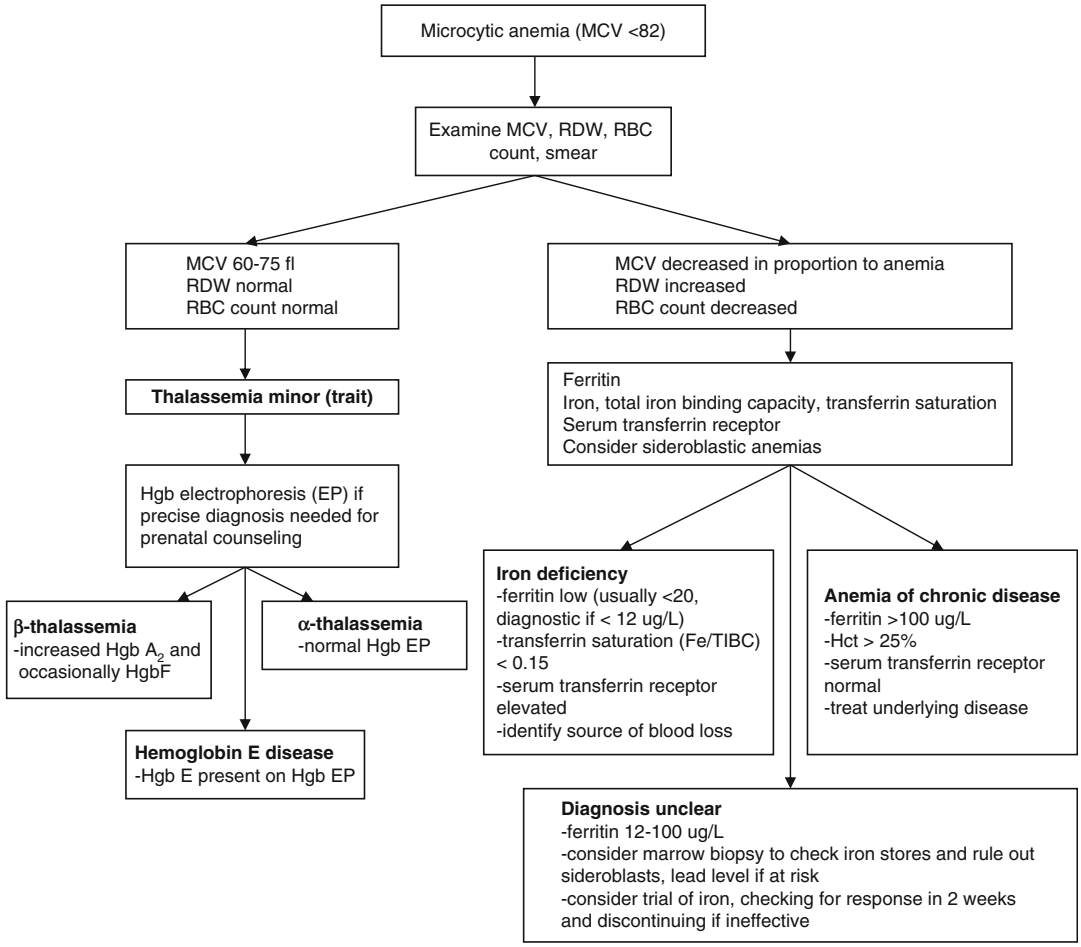

Fig. 1 Evaluation of microcytic anemia

A corrected reticulocyte percentage (also known as reticulocyte index) greater than 1 % indicates appropriate bone marrow response to anemia. If the value is less than 1 %, causes of hypoproliferative bone marrow should be sought. Increased reticulocyte counts are present in hemolysis and acute hemorrhage and response to treatment in anemias from other causes. An alternative to corrected reticulocyte percentage is the absolute reticulocyte count, which equals the reported reticulocyte percentage multiplied by the RBC count. The absolute reticulocyte count is normally 50,000–75,000/mm^3.

Peripheral Smear. Abnormalities in the peripheral smear, such as burr cells seen in renal failure or teardrop cells found in myelofibrosis, can assist in determining the etiology of anemia.

Other Laboratory Tests. Further laboratory testing may be warranted, depending on the above RBC indices and peripheral smear. Bone marrow biopsy is reserved for situations in which anemia remains unexplained or is suspected to arise from marrow dysfunction. Current research focuses on other RBC indices such as MCH, reticulocyte cell Hgb content, and reticulocyte maturity index and the role of genetics in diagnosing anemia [8]. Algorithms for evaluation of microcytic, normocytic, and macrocytic anemias are provided in Figs. 1, 2, and 3.

Microcytic Anemias

Iron Deficiency Anemia

IDA is probably the most common cause of anemia in the USA (Fig. 1). The recommended dietary allowance (RDA) for iron is 8 mg daily for men and 18 mg daily for women [9]. Daily requirements increase during pregnancy,

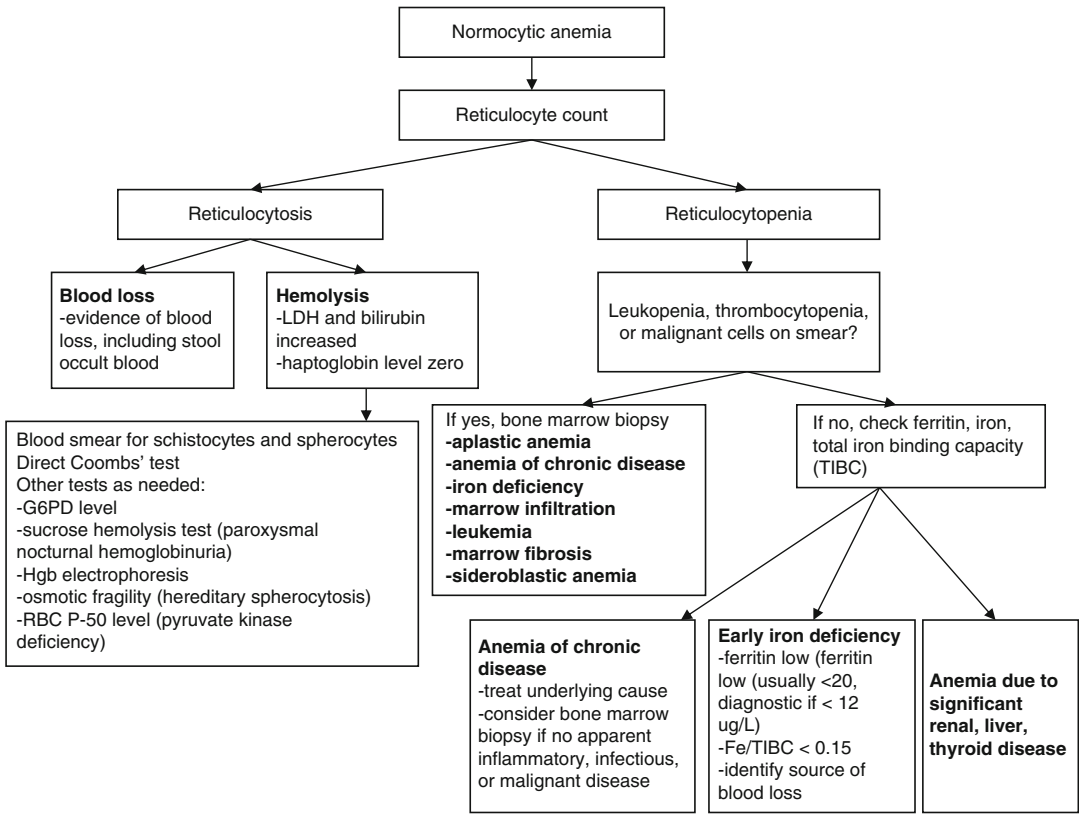

Fig. 2 Evaluation of normocytic anemia

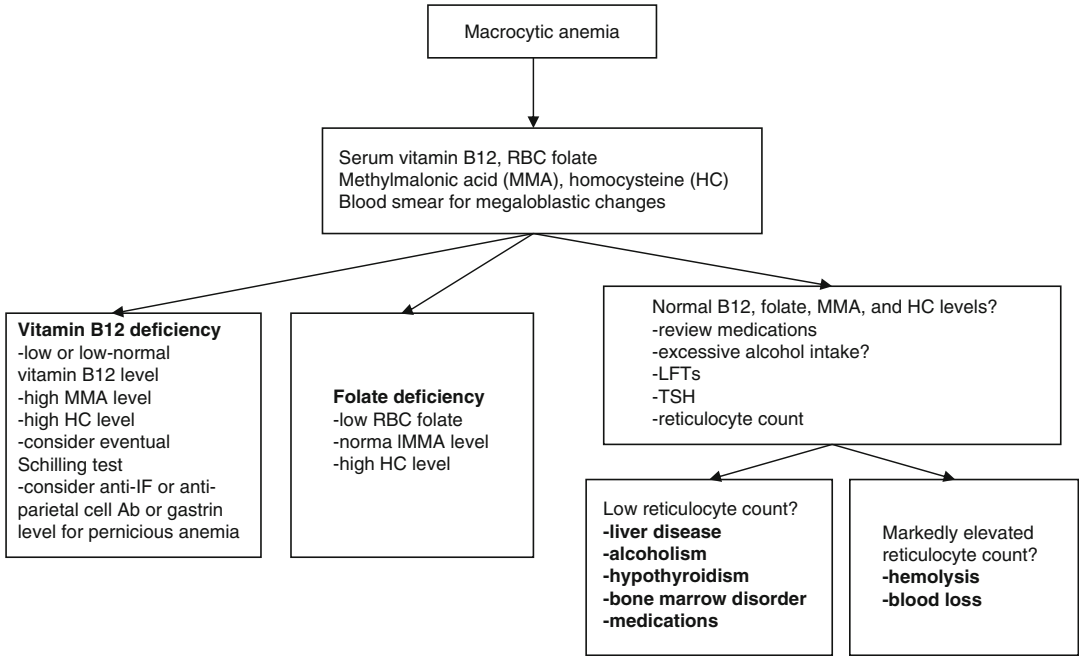

Fig. 3 Evaluation of macrocytic anemia

lactation, and adolescence. Meats, eggs, vegetables, legumes, and cereals are principal sources of iron in the American diet, with iron from meats being much more available for absorption than iron from other dietary sources.

In the USA, IDA accounts for approximately 40 % of anemia in children. Term, healthy infants have sufficient iron stores for at least the first 4 months of life. However, breast milk does not contain as much iron as does formula, so full-term infants who are exclusively or mostly breastfed may become iron deficient around 4–6 months of age until they receive sufficient iron through solid food sources. Therefore, iron supplementation of 1 mg/kg/day may be considered in these infants starting at 4 months of age until appropriate iron-containing complementary foods (including iron-fortified cereals) are introduced into the diet.

IDA may also be seen in older infants fed primarily with cow's milk because the iron content is low and cow's milk may displace other sources of iron in these infants' diets. Furthermore, the high levels of calcium and phosphorous in cow's milk can decrease iron absorption. Thus, the American Academy of Pediatrics recommends screening for anemia in all infants around 12 months of age [10]. A serum ferritin and C-reactive protein level (CRP) should be checked. Elevations of both ferritin and CRP can occur in the setting of inflammation. On the other hand, a low serum ferritin (<10 ug/L) confirms IDA, and these infants should be treated appropriately. Alternatively, infants with mild anemia (10–11 dL/g) can undergo a trial of iron supplementation for 1 month, and a repeat Hgb showing an appropriate rise of 1 dL/g would confirm IDA [10].

Other populations that may develop IDA include children and adolescents whose iron needs are increased due to their rapidly growing bodies in conjunction with poor iron intake. Females lose iron in menstrual blood and can become iron deficient if their bleeding outpaces their iron intake. Pregnancy places additional demands on a woman's iron stores as the placenta and fetus require iron, and blood is lost during childbirth. Obesity can predispose to IDA due to increased inflammation from adipose tissue and subsequent increased production of hepcidin, which directly impairs absorption of iron and iron availability for erythropoiesis. Patients with

a history of bariatric surgery are at risk of IDA given their history of obesity and possible malabsorption resulting from the surgery itself [11]. IDA is also seen in decreased absorption states such as celiac disease and gastrectomy.

In men and postmenopausal women, GI blood loss is the most likely cause of IDA. In these patients, a diligent search for occult GI bleeding is imperative when another source of bleeding is not readily appreciated. This should include upper and lower endoscopy with small bowel biopsy. Radiologic tests may substitute if endoscopy is not practical. In over 1/3 of patients with IDA, no source of blood loss will be found despite this evaluation [12]. In these patients, prognosis is good, with anemia resolving in more than 2/3 without recurrence [13]. Further search for source of GI blood loss is required only for persistent bleeding or severe anemia.

Physician examination may reveal glossitis and angular stomatitis. Esophageal webs, splenomegaly, and koilonychias (spoon-shaped nails) rarely occur. Patients may complain of RLS. Although the relationship is unclear, one study showed 24 % of patients with IDA also had RLS [14].

The most sensitive and specific laboratory test for IDA is serum ferritin, which reflects iron stores. While a ferritin below 12 ug/L is diagnostic, a workup for IDA should be considered in patients with ferritins of 13–20 ug/L since a significant number of these patients will have IDA. Since ferritin is an acute phase reactant, falsely normal levels may occur with coexisting inflammatory conditions. Normal ferritin values also increase with age and must be considered when evaluating anemia in an older adult. Nonetheless, a ferritin level above 100 ug/L practically rules out IDA [15]. A decreased serum iron and increased total iron-binding capacity (TIBC) are helpful but less reliable indicators of IDA. The transferrin saturation (iron/TIBC) should be less than 0.15, but this ratio may be reduced in ACD as well. The MCV is usually normal in early iron deficiency and typically decreases after the Hct drops. The MCV then changes in proportion to the severity of anemia. The RDW is often increased. Although not as widely available, soluble serum transferrin receptor (TfR) rises in IDA and may assist diagnosis in difficult cases, although an increase in TfR may also be seen in increased or ineffective erythropoiesis [16, 17]. The transferrin receptor-ferritin index (ratio of sTfR to the logarithm of serum ferritin) may also play a role in these difficult cases, with a value >2 suggesting IDA and a value <1.0 indicating ACD [17].

Occasionally, ferritin values fall in the indeterminate range of 12–100 ug/L, and the diagnosis remains uncertain. Bone marrow biopsy is the gold standard to determine iron stores but is rarely necessary. An alternative is a several week trial of iron replacement. Reticulocytosis should peak after 1 week, and the Hct should normalize in about a month. If no response to therapy occurs, iron should be discontinued to prevent potential iron overload and iron therapy side effects.

Oral iron replacement is available in ferrous and ferric forms. Ferrous forms are preferred due to superior absorption and include ferrous sulfate, gluconate, and fumarate. Although most patients with IDA may not need this much, ferrous sulfate 325 mg TID (65 mg of which is elemental iron) is the cheapest and provides the theoretically needed 150–200 mg of elemental iron per day in patients with IDA. Some studies suggest that much less iron supplementation is needed in patients with IDA as their GI tracts absorb more iron after becoming iron deficient. Thus, as little as 60 mg elemental iron once or twice a week may suffice if the patient is unable to tolerate daily dosing [18]. Although Hct should normalize in a few weeks, iron replacement should continue until ferritin reaches 50 ug/L or at least 4–6 months. Many patients experience side effects of nausea, constipation, diarrhea, or abdominal pain as a result of activated hydroxyl radicals released during the oxidation of ferrous compounds within the lumen of the gut or the mucosa [6]. Enteric-coated iron preparations are meant to decrease these symptoms but are not well absorbed and should be avoided. To minimize these effects, iron may be started once a day and titrated up. In addition, iron may be taken with food, although this can decrease absorption by 40–66 % [19]. Taking iron with vitamin C may help increase absorption [20]. Liquid iron preparations may be tried. Despite these measures, 10–20 % of patients will

not tolerate oral iron replacement [21]. Bran, eggs, milk, tea, caffeine, calcium-rich antacids, H_2-blockers, proton pump inhibitors, and tetracycline can interfere with iron absorption and should not be taken at the same time. Also, iron supplementation can interfere with the absorption of other medications, including quinolones, tetracycline, thyroid hormone, levodopa, methyldopa, and penicillamine.

Most patients respond well to oral replacement of iron. Treatment failures may result from poor adherence, continued blood loss, interfering substances listed above, or gastrointestinal disturbances limiting absorption. In the rare case where poor absorption or severe intolerance to iron cannot be overcome, parenteral replacement may be needed. Iron dextran may be given IV or as a painful IM injection. The total dose (mg) required to replenish stores equals:

$$0.3 \times \text{body weight (lb)} \times (100 - \text{Hgb [g/dL]} \times 100)/14.8$$

Adverse reactions include headache, flushing, dyspnea, nausea, vomiting, fever, hypotension, seizures, and chest, back, and abdominal pain. Urticaria and anaphylaxis can occur. A test dose (0.5 ml = 12.5 mg) should be given to determine whether anaphylaxis will occur. If tolerated, the remainder of the dose may be given up to a maximum daily dose of 100 mg over 2 min or more. If possible, intravenous iron is preferred over intramuscular due to a lower incidence of local reactions and more consistent absorption.

Thalassemia

The thalassemias are inherited disorders of hemoglobin synthesis that are more common in people from the Mediterranean, Asia, and Africa. The rare thalassemia majors cause severe anemia and are discovered early in life. Family physicians are more likely to encounter thalassemia trait (thalassemia minor) occurring in individuals heterozygous for alpha or beta globin chain mutations.

Thalassemia trait should be suspected in an asymptomatic patient with mild anemia and a disproportionately low MCV (56–74 fl). The RDW is usually normal, and the RBC count is normal or increased by 10–20 %. Iron studies are normal unless concomitant IDA is present. Blood smear may show target cells, ovalocytes, and basophilic stippling. If a precise diagnosis is required (e.g., for prenatal counseling), hemoglobin electrophoresis may be performed. In beta thalassemia trait, elevated levels of Hgb A2 and occasionally Hgb F will be seen. In alpha thalassemia trait, the hemoglobin electrophoresis will be normal, and the diagnosis is made by exclusion. It is important to determine the etiology of anemia in these patients as treatment with iron therapy is unnecessary and potentially harmful in patients with thalassemia trait who do not have IDA.

Hemoglobin E

Hgb E has a prevalence of 5–30 % in certain groups from Southeast Asia. The heterozygote has mild microcytosis and normal Hct. Homozygotes have marked microcytosis (MCV 60–70 fl) and mild anemia. Target cells may be present on peripheral smear. Hgb electrophoresis reveals the presence of Hgb E, establishing the diagnosis. Patients who have both Hgb E and beta thalassemia develop severe transfusion-dependent anemias.

Sideroblastic Anemia

Sideroblastic anemias are a heterogeneous group of disorders in which ringed sideroblasts are found on bone marrow staining. Sideroblastic anemia may be X linked or due to toxins or medications (lead, alcohol, isoniazid, chloramphenicol, chemotherapy). It may be related to neoplastic, endocrine, or inflammatory diseases or a part of myelodysplastic syndrome. The MCV is usually low but may range from low to high. Iron saturation and ferritin are normal to high. Marrow examination is diagnostic, and treatment is aimed at the underlying cause. In the case of lead poisoning, anemia is microcytic, and basophilic stippling may be seen on peripheral smear. This diagnosis should be suspected and

serum lead level tested in high-risk groups such as children ingesting paint, soil, and dust and adults with occupational exposure.

Normocytic Anemias

The absolute reticulocyte count or corrected reticulocyte percentage is important in determining the cause of a normocytic anemia (Fig. 2).

Normocytic Anemia with Elevated Reticulocytes

Acute Blood Loss. Acute blood loss is usually obvious but can be missed in cases such as hip fractures and retroperitoneal or pulmonary hemorrhages. The true degree of anemia may not be revealed in the Hct at first, since RBCs and plasma are lost equally. It may take several days for equilibration of blood volume and Hct to fully reflect the degree of bleeding.

Hemolysis. There are many causes of hemolytic anemia (Table 2). Laboratory values consistent with hemolysis include elevated serum lactate dehydrogenase (LDH) and indirect bilirubin. Haptoglobin, a plasma protein that binds and clears Hgb, drops precipitously in the presence of hemolysis. If hemolysis is suspected, the peripheral smear should be examined for schistocytes (mechanical hemolysis) and spherocytes (autoimmune hemolysis or hereditary spherocytosis). A direct Coombs' test will reveal an autoimmune basis for hemolysis. Further, confirmatory testing may be performed as appropriate (Fig. 2), usually with the guidance of a hematologist. Treatment of hemolytic anemia is directed at the underlying cause and providing supportive care. Corticosteroids and splenectomy may be indicated for specific causes.

Table 2 Causes of hemolysis

Intrinsic (defect in RBCs)	Extrinsic (defect external to RBCs)
Hemoglobinopathies	Immune
Sickle syndromes	Autoimmune
Unstable hemoglobins	Lymphoproliferative
Methemoglobinemia	Malignancy
Membrane disorders	Collagen vascular disorders
Paroxysmal nocturnal hemoglobinuria	Drug induced (methyldopa, procainamide, quinidine, levodopa, sulfas, penicillin, NSAIDS)
Hereditary spherocytosis	Mechanical
Elliptocytosis	Disseminated intravascular coagulation (DIC)
Pyropoikilocytosis	Thrombotic thrombocytopenia purpura (TTP)
Stomatocytosis	Hemolytic uremic syndrome (HUS)
Enzyme deficiencies	Prosthetic heart valves
Glucose-6-phosphate dehydrogenase (G-6-PD)	Disseminated neoplasms
Pyruvate kinase	Burns
Glucose phosphate isomerase	Malignant hypertension
Congenital erythropoietic porphyria	Vasculitis
	Severe hypophosphatemia
	Physical activity ("march" hemoglobinuria)
	Strenuous exercise
	Hypersplenism
	Infections
	Clostridium, *Plasmodium*, *Borrelia*, *Mycoplasma*, *Babesia*, *Hemophilus*, *Bartonella*
	Bites
	Snakes
	Spiders

Normocytic Anemias with Decreased Reticulocytes

Anemia of Chronic Disease. ACD, also called anemia of chronic inflammation (ACI), results from chronic inflammatory disorders, infections, and malignancies. ACD is the second most common cause of anemia after iron deficiency. It is probably the most common form of anemia in the elderly [22]. The pathogenesis of ACD is

multifactorial and not fully understood. Proposed mechanisms include reduction in RBC life span, impaired utilization of iron stores, and a relative erythropoietin deficiency. Although the anemia is customarily normocytic, it can be microcytic in 30–50 % of cases [23]. The degree of anemia is usually mild, with Hgb between 7 and 11 g/dl. The serum iron, TIBC, and transferrin saturation are usually low and not helpful in distinguishing ACD from IDA. More useful is the ferritin level, which is normal or high in ACD. Ferritin greater than 100 ug/L essentially rules out IDA, whereas levels less than 12 ug/L are diagnostic of IDA. In cases of uncertain ferritin levels (12–100 ug/L), a brief therapeutic trial of iron or a bone marrow biopsy may help with the diagnosis. Normal TfR levels may be useful in diagnosing ACD due to the suppression of TfR by inflammatory cytokines [15].

Treatment of ACD is directed toward the management of the underlying disorder. Erythropoietin plus iron supplementation is effective in raising Hct in certain cases. Iron treatment by itself is not indicated for ACD since iron stores are adequate. However, if the anemia is more severe than expected, one should search for a coexisting cause. For example, a patient with rheumatoid arthritis may develop concomitant IDA from GI blood loss due to chronic NSAID use.

Chronic Kidney Disease. Anemia occurs frequently in chronic kidney disease (CKD) due primarily to the kidney's inability to secrete erythropoietin. Generally, the creatinine is above 3 mg/dl or the estimated glomerular filtration rate (eGFR) is less than 30 ml/min/1.73 m^2. The peripheral smear is usually normal, but burr cells can be seen. The ferritin is typically increased. If a low to low-normal ferritin is noted, concomitant IDA should be entertained. In fact, many patients with end-stage kidney disease may suffer from "functional iron deficiency." The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) recommends considering iron repletion in patients with CKD with anemia and serum transferrin saturation <30 % and ferritin <500 μg/L [24].

Therapy consists of ameliorating the renal disease and administering erythropoiesis-stimulating agents (ESAs), namely, erythropoietin and darbepoetin. ESA should be considered for all non-hemodialysis patients with CKD and Hgb < 10 g/dl, with a goal Hgb of 10–11.5 g/dl. Initial dosing of ESA is based on the patient's Hgb concentration, body weight, and clinical circumstances, and it is adjusted based on the patient's response to treatment. The FDA recommends starting epoetin alfa at 50–100 units/kg three times per week; however, more commonly, it is dosed at 10,000 units weekly or 20,000 units every other week. Patients with concomitant IDA should have iron repleted prior to and during ESA therapy in order to prevent worsening IDA and enhance erythropoiesis. Iron stores should be assessed at least every 3 months during treatment [24]. The treatment and dosing of ESA with iron supplementation may be performed in consultation with a hematologist and/or nephrologist. Hemodialysis may improve RBC production, but ESA is the mainstay of treatment, even before dialysis is required. Complications of ESAs include increased blood pressure.

Chronic Liver Disease. Chronic liver disease causes a normocytic or occasionally macrocytic anemia. Target cells can be seen on peripheral smear. Spur cells are seen in severe liver failure. Treatment is directed at improving liver function. Alcoholics with liver disease have additional causes for anemia that are discussed under non-megaloblastic macrocytic anemias.

Endocrine Disease. Various endocrine diseases such as hypothyroidism, hyperthyroidism, hypogonadism, hypopituitarism, hyperparathyroidism, and Addison's disease are associated with anemia. The anemia is corrected with treatment of the underlying endocrine problem.

Aplastic Anemia. Aplastic anemia is due to an injury or destruction of a common pluripotential stem cell resulting in pancytopenia. Bone marrow biopsy reveals severe hypoplasia and fatty infiltration. In the USA, approximately half the cases are idiopathic. Other causes include viral infections (HIV, hepatitis, EBV), drugs and chemicals (chemotherapy, benzene, chloramphenicol), radiation, pregnancy, immune diseases (eosinophilic fasciitis, hypoimmunoglobulinemia, thymoma, thymic carcinoma, graft-vs.-host disease),

paroxysmal nocturnal hemoglobinuria, systemic lupus erythematosus, and inherited disorders.

Treatment includes managing the underlying cause and supportive care in conjunction with a hematologist. Judicious use of transfusions may be needed if the anemia is severe. Immunosuppressive therapy and bone marrow transplantation are indicated in certain cases.

Myelophthisic Anemia. Myelophthisic anemias result from bone marrow infiltration by invading tumor cells (hematologic malignancies or solid tumor metastases), infectious agents (tuberculosis, fungal infections), or granulomas (sarcoidosis). Less common causes include lipid storage diseases, osteopetrosis, and myelofibrosis. Treatment is directed at the underlying cause.

Red Cell Dysplasia. Pure red cell dysplasias involve a selective failure of erythropoiesis. The granulocyte and platelet counts are normal. Red cell dysplasias share many causes with aplastic and myelophthisic anemia, including malignancies, connective tissue disorders, infections, and drugs. There is an idiopathic form and a congenital form. One infection that specifically targets red cell production is parvovirus B19. This virus also causes erythema infectiosum ("fifth" disease), an acute polyarthropathy syndrome, and hydrops fetalis. Anemia results from parvovirus B19 infection mostly in those with chronic hemolysis, by suppressing erythropoiesis and disrupting a tenuous balance needed to keep up with RBC destruction. In this situation, anemia can be profound but is usually self-limited. Parvovirus B19 infections may become chronic in immunosuppressed individuals who cannot form antibodies to the virus. Treatment concepts for red cell aplasia are similar to treatments for aplastic anemia.

Myelodysplastic Syndromes. The myelodysplastic syndromes (MDSs) are a group of clonal hematologic diseases of unknown etiology that result in the inability of bone marrow to produce adequate erythrocytes, leukocytes, platelets, or some combination of these. Patients are usually over 60 years of age and have an increased risk for leukemia. MDS may account for as much as 15–20 % of anemia in the elderly [2]. Bone marrow biopsy is diagnostic, revealing characteristic dysplastic blood precursor cells. Treatment is largely supportive.

Macrocytic Anemias

Macrocytic anemias may be separated into megaloblastic and non-megaloblastic types, based on peripheral smear findings (Table 1) (Fig. 3). A sensitive and specific sign of megaloblastic anemia is hypersegmented neutrophils, in which neutrophils contain nuclei with more than five lobes. A marked elevation of MCV (>120 fl) is also highly suggestive of megaloblastosis. RBCs of megaloblastic anemias, in addition to being increased in size, are often oval in shape (macroovalocytes).

Most macrocytosis, however, results from non-megaloblastic causes. Drug therapy and alcoholism may account for >50 % of macrocytosis, whereas vitamin B12 and folate deficiencies may be responsible for only 6 % of cases [25].

Megaloblastic Anemias

Vitamin B12 Deficiency. Vitamin B12 (cobalamin) is ingested from primarily animal sources, including meats, eggs, and dairy products. The US RDA of vitamin B12 increases with age and is 2.4 ug daily for adults. A typical Western diet provides 5–30 ug/day. After ingestion, B12 is bound by intrinsic factor, which is produced by gastric parietal cells. Bound vitamin is absorbed in the terminal ileum. Body stores of vitamin B12 total 2,000–5,000 ug. Thus, B12 deficiency takes years to develop and rarely occurs from dietary insufficiency except in strict vegans. The majority of B12 deficiency is due to pernicious anemia, which occurs primarily in the elderly and is most often due to autoimmune atrophy of the gastric mucosa and intrinsic factor deficiency. Less often, pernicious anemia can be due to *H. pylori* infections or Zollinger-Ellison syndrome. Other causes of B12 deficiency include gastric and ileal surgeries, including gastric bypass surgery and ileal absorption problems such as Crohn's disease, sprue, and tapeworm infection.

Signs and symptoms of B12 deficiency include glossitis, sore mouth, and GI disturbances such as constipation, diarrhea, and indigestion. Neurologic symptoms such as paresthesias of the

extremities and subacute combined degeneration (loss of lower extremity vibration and position sense) may occur. Dementia and subtle neuropsychiatric changes may be present. Importantly, anemia or macrocytosis is absent in 28 % of patients with neurologic abnormalities due to B12 deficiency [26].

In addition to peripheral smear changes of hypersegmented neutrophils and macroovalocytes, laboratory findings include a low B12 level (<200 pg/ml) and reticulocyte count. However, low-normal B12 levels (<350 pg/ml) are present in many patients with neurologic disease or anemia, so further workup may be indicated if the diagnosis is still suspected. Falsely low B12 levels may be found in folate deficiency, pregnancy, and myeloma. Elevated serum methylmalonic acid (MMA) levels are highly sensitive and essentially rule out B12 deficiency if normal. In one study, elevated MMA levels occurred in 98 % of cases of clinically defined B12 deficiency. Falsely elevated levels occur in kidney disease and hypovolemia, and spot urine MMA levels may be superior in this setting. Homocysteine level rises with B12 deficiency (96 % of cases in one study) but is less specific, occurring in folate deficiency and kidney disease as well [27–29]. Occasionally, a mild thrombocytopenia and leukopenia, along with an elevated LDH and indirect bilirubin from ineffective erythropoiesis, are present.

Traditionally, the Schilling test was performed to determine the etiology of B12 deficiency. It measures 24-h urinary excretion of radiolabeled B12 given orally and distinguishes pernicious anemia from bacterial overgrowth and other absorption problems. This test is not commonly utilized as it is expensive, difficult to perform properly, and no longer available in many centers. Antibodies to intrinsic factor may be measured and are the preferred test for diagnosing pernicious anemia. These antibodies are highly specific for pernicious anemia but present in only about 50 % of cases. Antibodies to gastric parietal cells are found in about 85 % of cases of pernicious anemia but also in 3–10 % of healthy persons [29]. Extremely elevated serum gastrin levels and low pepsinogen 1 levels also suggest pernicious anemia.

B12 replacement regimens vary. One common method is 1,000 ug vitamin B12 IM daily for 1 week, then weekly for 1 month, and then every 1–3 months. The Hct should return to normal in 2 months. Failure to normalize should trigger a search for coexisting iron deficiency, which occurs in up to one third of patients. Six months or more may be needed for neurologic improvement, and up to 80 % of patients will have at least partial resolution of neurologic manifestations. An alternative to parenteral B12 is high-dose oral therapy. Patients with pernicious anemia can absorb 1–2 % of oral B12 without the addition of intrinsic factor, so treatment with daily oral B12 1,000–2,000 ug can be considered in adherent patients [30]. B12 maintenance can also be accomplished with an intranasal gel preparation 500 ug once weekly, although this form is more costly than parenteral and oral forms. Treatment should continue indefinitely as the deficiency will likely return unless a reversible cause is identified and addressed.

Folate Deficiency. Folate is found in a wide variety of unprocessed foods. Especially rich sources include green leafy vegetables, citrus fruits, liver, and certain beans and nuts. The RDA for folate is about 200 ug daily and is increased to 400 ug in pregnancy. In contrast to vitamin B12, folate stores remain adequate for only 2–4 months, so folate deficiency anemia is often the result of inadequate dietary intake. The typical Western diet provides only 200–300 ug of folate daily. Persons at risk for folate deficiency include malnourished alcoholics, neglected elderly, and the homeless. Patients who are pregnant or have certain malabsorption disorders are also at risk. Impaired absorption may occur in patients taking oral contraceptives, metformin, or anticonvulsants, such as phenobarbital and phenytoin. Cirrhosis can lead to deficiency through decreased storage and metabolism capabilities of the liver. Dialysis can cause loss of folate and deficiency.

The clinical findings of folate deficiency are similar to B12 deficiency except neurologic symptoms are generally absent. The laboratory findings are similar except that the homocysteine level alone is elevated while MMA remains normal. The serum folate can rise to normal after a recent folate-rich meal, vitamin ingestion, or

hemolysis, so serum folate should not be used for diagnosis. Although expensive, RBC folate level is felt to be more accurate. Confirmation with homocysteine levels should be obtained if the diagnosis is suspected.

Treatment is aimed at the underlying problem. Replacement is usually 1 mg orally daily. If present, concurrent vitamin B12 deficiency must be treated as well, because folate replacement can resolve hematologic abnormalities while permitting neurologic damage from vitamin B12 deficiency to progress.

Drugs. Certain drugs cause megaloblastic anemia. Most common causes are chemotherapy agents. Infrequent causes are phenytoin, sulfasalazine, zidovudine, trimethoprim, pyrimethamine, methotrexate, triamterene, sulfa compounds, and oral contraceptives.

Non-Megaloblastic Anemias

Alcoholism. The most common cause of non-megaloblastic macrocytic anemia is alcoholism. Anemia in alcoholics may arise from multiple causes. Alcohol suppresses erythropoiesis and decreases folate absorption in patients whose diets are often poor. Alcoholics can lose blood from varices and ulcers. Anemia is worsened if liver failure occurs. Moreover, alcoholics are prone to develop sideroblastic or hemolytic anemia. They are also at increased risk for developing infections that can lead to ACD. Comprehensive therapy includes reduction of alcohol intake, folate supplementation, and treatment of complications.

Miscellaneous. The anemia of hypothyroidism, chronic liver disease, postsplenectomy, and primary bone marrow disorders may be macrocytic instead of normocytic. Hemolytic anemia or hemorrhage can result in macrocytosis when reticulocytes, which are larger than normal RBCs, are markedly increased. Certain drugs occasionally cause non-megaloblastic macrocytic anemia. Spurious macrocytosis, although rare, must also be considered due to cold agglutinins causing the RBCs to clump and appear larger to automated counters. Other causes include hyperglycemia causing RBCs to swell when diluted during blood processing or leukocytosis leading to increased blood sample turbidity with a subsequent overestimation in cell size by the machine [31].

Summary

Discovery of anemia should lead the physician to investigate the underlying cause of anemia. Conversely, it may be reasonable to check for anemia in patients who develop certain acute or chronic medical conditions. The history and physical examination combined with the CBC, peripheral smear, and reticulocyte count reveal the etiology in most cases. However, it is not uncommon to find multifactorial causes for a patient's anemia. If the type of anemia remains unclear or there is additional evidence of marrow dysfunction (pancytopenia), a bone marrow biopsy and hematology consultation may be indicated.

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