PORTRAITS OF ANEMIA: UNDERSTANDING A PERVASIVE AND PERSISTENT PROBLEM

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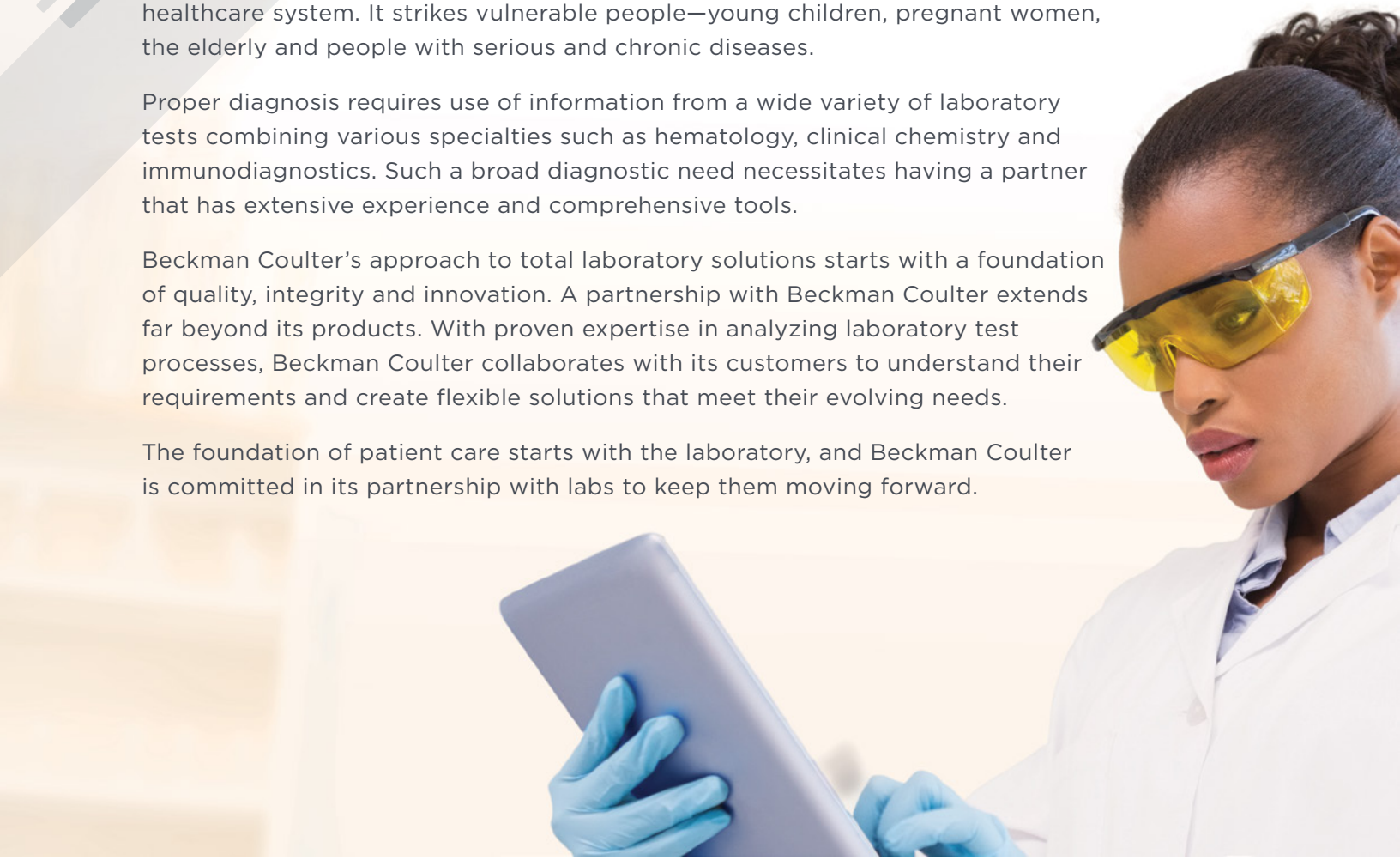
Move healthcare forward.

Anemia is a globally pervasive, persistent problem and a significant burden to the healthcare system. It strikes vulnerable people—young children, pregnant women, the elderly and people with serious and chronic diseases.

Proper diagnosis requires use of information from a wide variety of laboratory tests combining various specialties such as hematology, clinical chemistry and immunodiagnostics. Such a broad diagnostic need necessitates having a partner that has extensive experience and comprehensive tools.

Beckman Coulter's approach to total laboratory solutions starts with a foundation of quality, integrity and innovation. A partnership with Beckman Coulter extends far beyond its products. With proven expertise in analyzing laboratory test processes, Beckman Coulter collaborates with its customers to understand their requirements and create flexible solutions that meet their evolving needs.

The foundation of patient care starts with the laboratory, and Beckman Coulter is committed in its partnership with labs to keep them moving forward.



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Anemia: a Public Health Issue

Anemia has been recognized by the World Health Organization (WHO) as a "significant global public-health problem affecting both developing and developed countries."[1] In the broadest terms, it is a condition characterized by a low concentration of hemoglobin in the blood, impairing quality of life and potentially leading to additional health complications or life-threatening conditions.

Anemia is a very complex disease due to the fact that there are multiple specific types of anemia (many of which often coexist) that can result from a wide variety of causes. There are five major types of anemia in which various causes can be defined:

- Iron-deficiency anemia (IDA)
- Anemia of chronic disease (ACD)
- Vitamin-deficiency anemia
- Anemia of cancer
- Anemia of renal failure

Assessing the prevalence of anemia in the world is difficult, since yearly worldwide statistics are unavailable, but a recent report from the WHO gives an indication of the problem's severity and the extent of this worldwide healthcare burden. The report reveals that women and preschool-aged children are particularly affected (Table 1).[1]

Table 1: Anemia prevalence and number of individuals affected in preschool-age children, pregnant women and non-pregnant women in each WHO region

WHO Region	Preschool-age Children*		Pregnant Women*		Non-pregnant Women*	
	Prevalence (%)	No. Affected (millions)	Prevalence (%)	No. Affected (millions)	Prevalence (%)	No. Affected (millions)
Africa	67.6	83.5	57.1	17.2	47.5	69.9
Americas	29.3	23.1	24.1	3.9	17.8	39
Southeast Asia	65.5	115.3	48.2	18.1	45.7	182
Europe	21.7	11.1	25.1	2.6	19	40.8
Eastern Mediterra-nean	46.7	.08	44.2	7.1	32.4	39.8
Western Pacific	23.1	27.4	30.7	7.6	21.5	97
Global	**47.4**	**293.1**	**41.8**	**56.4**	**30.2**	**468.4**

*Population subgroups: Preschool-age children (0–4.99 yrs); pregnant women (no age range defined); non-pregnant women (15–49.99 yrs).

Adapted from Worldwide Prevalence of Anemia; 1993–2005 WHO Global Database on Anemia 2008.

In developed countries, with an increased aging population, there is a high prevalence of anemia being reported among the elderly (Table 2), which creates an important health issue and a growing concern.[2]

Table 2: Distribution of types of anemia in the elderly

	No. in the United States	Type %	All Anemia %
With nutrient deficiency			
Iron only	467,000	48.3	16.6
Folate only	181,000	18.8	6.4
B12 only	166,000	17.2	5.9
Folate and B12	56,000	5.8	2
Iron with Folate or B12 (or both)	95,000	9.9	3.4
Total	965,000	100	34.3
Without nutrient deficiency			
Renal insufficiencies only	230,000	12.4	8.2
ACI, no renal insufficiencies	554,000	30	19.7
Renal insufficiencies and ACI	120,000	6.5	4.3
UA	945,000	51.1	33.6
Total	1,849,000	100	65.7
Total (all anemia)	**2,814,000**	**N/A**	**100**

ACI: anemia of chronic infection
UA: unexplained anemia

Distribution of anemia types in persons 65 years and older. United States: NHANES III, phase 2, 1991–1994.

A 2004 publication demonstrated that, in the majority of anemic patients over the age of 65, the root cause of the anemia remains unknown, reflecting the difficulties of accurate anemia diagnosis.[2] When a correct diagnosis is achieved, the most frequent types of anemia are ACD and IDA (Table 3). Anemia related to vitamin B12 and/or folate deficiency, also known as vitamin-deficiency anemia, is also common, particularly in the elderly. In elderly patients, early diagnosis of the specific type of anemia is critical. Failing to do so could lead to delays in proper treatments for conditions which directly affect cardiac, physical and cognitive functions.[3]

Table 3: Prevalence of different types of anemia in patients >65 years

Type of Anemia	Prevalence %
Combined	35
Chronic Disease and Cancer	24
Iron Deficiency	17
Vitamin Deficiency	14
Renal Failure	10

Anemia: the Value of the Laboratory

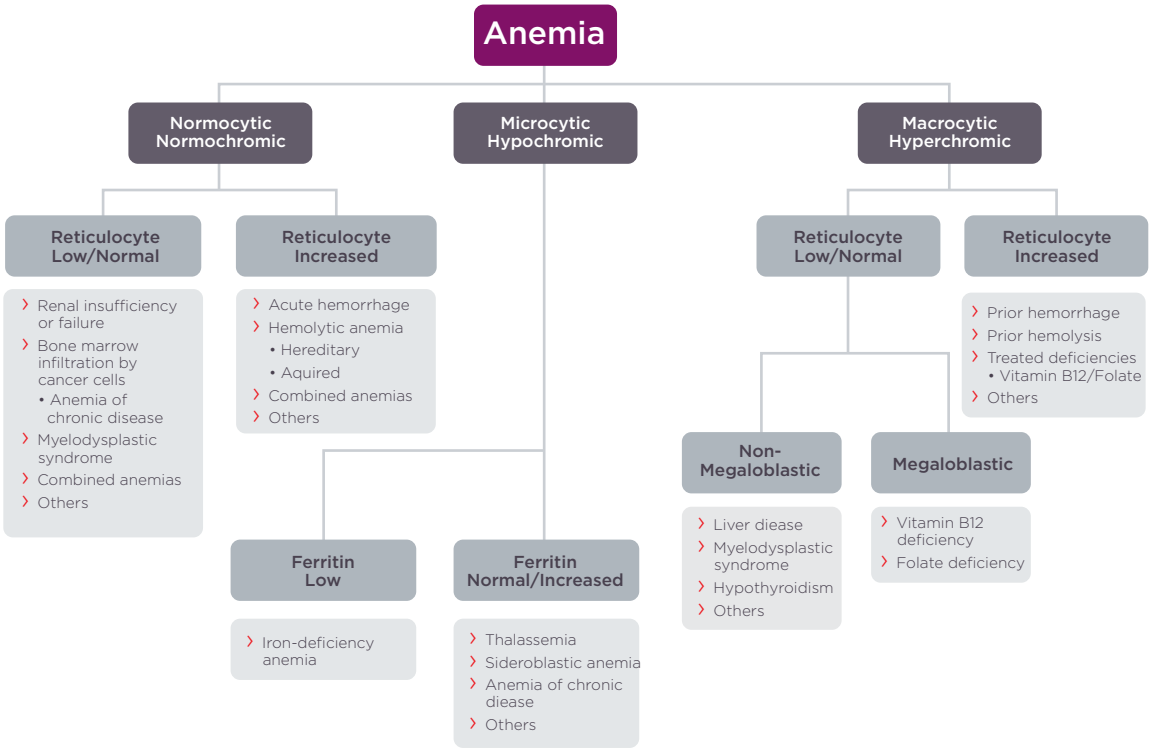
Though anemia itself is complex, in most cases, it may be diagnosed easily and correctly with the help of a thorough medical history, clinical examination and, most importantly, laboratory tests that are specific for diagnosing anemia in all its forms.

Initially, routine hematology analysis such as hemoglobin concentration, red cell count and red cell indices—such as mean corpuscular volume (MCV) and mean corpuscular hemoglobin corpuscular (MCHC)—will provide the first indications to guide the diagnosis toward a specific type of anemia (Figure 1).[4]

For a more in-depth investigation, additional laboratory tests—including increased hematology parameters (such as reticulocytes), clinical chemistry (serum iron, transferrin, iron binding capacity) and immunodiagnostic assays (ferritin, sTfR, folate, B12, intrinsic factor Ab)—are used by physicians for the differential and final diagnosis of a specific type of anemia.

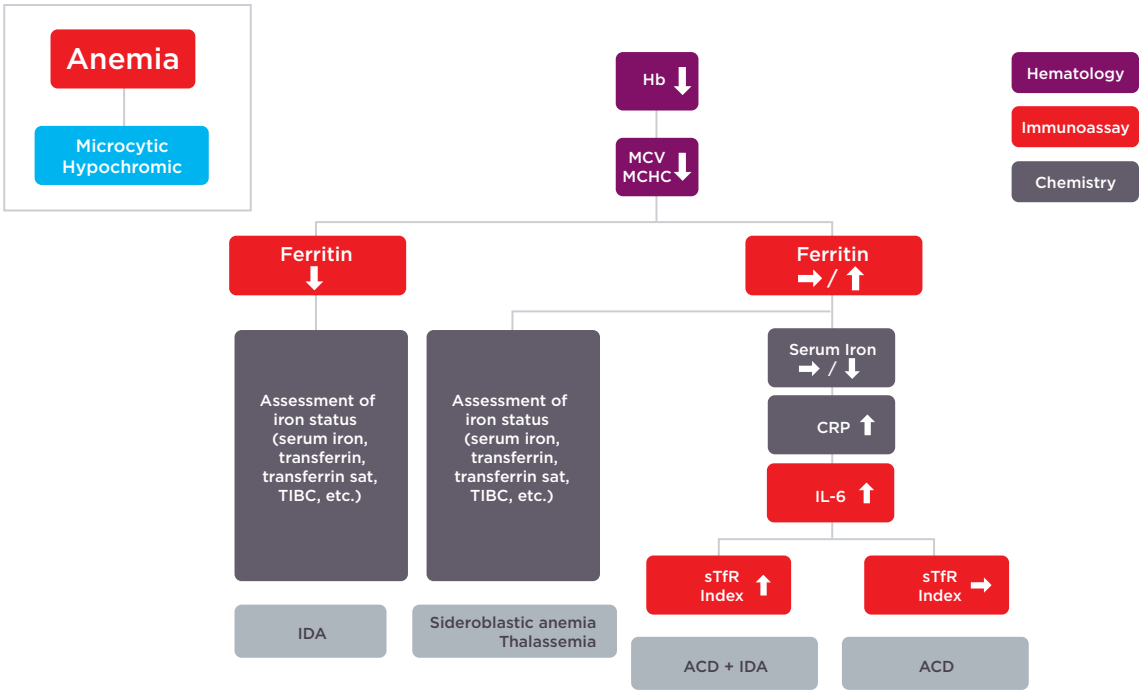
Once the cause has been identified, appropriate treatment (monitored by laboratory testing) can be initiated to resolve the anemia and help people live healthier, fuller lives.

Figure 1: Simplified and general model of potential anemia diagnosis



Adapted with modifications from Wintrobe's Clinical Hematology, 9th ed., 1993.

Iron-Deficiency Anemia (IDA) and Anemia of Chronic Disease (ACD)



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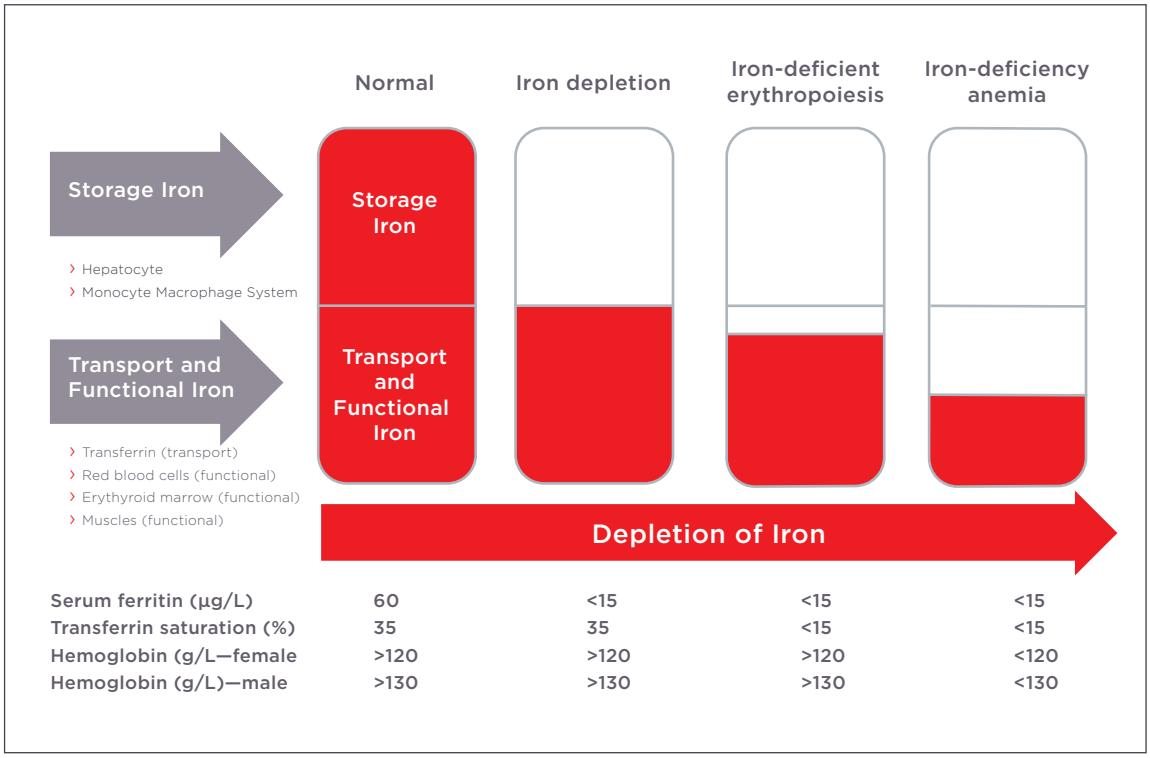
Iron-deficiency Anemia (IDA)

The iron required for the production of hemoglobin in the body is bound to ferritin molecules that are present in the hepatocytes and monocyte macrophage system. The transferrin molecule is required for the transport of iron from iron stores to the functional compartments where it is used: marrow, red blood cells and muscles.

Laboratory information is important to aid in evaluating the degree of iron deficiency (Figure 2).[5] Following progressive iron depletion, the iron storage compartment is first affected with a decrease in serum ferritin concentration. Next, the transport and functional compartments are depleted, leading to iron-deficient erythropoiesis reflected by a decrease in transferrin saturation level. Finally, full IDA is indicated by a decrease in hemoglobin concentration. Red blood cell (RBC) morphology parameters on hematology instruments are used to detect microcytic hypochromic RBC, which are often associated with IDA.

Figure 2: Potential clinical results profile in progressive depletion of iron



Modified from Sarah Cusick, P.h.D, Centers for Diseases Control and Prevention, 2008.

Iron-deficiency anemia is known to have detrimental health implications, particularly for mothers and young children. Globally, iron deficiency is the most significant contributor to the onset of anemia. It is generally assumed that 50% of all anemia cases are fully or partly due to iron deficiency.[6, 7] Though this proportion may vary among population groups and geographies,[6, 7] the fact remains that IDA is a major worldwide concern.

One of the more at-risk groups for IDA is pregnant women. It is estimated that 90% of anemia cases in pregnant women are specifically due to iron deficiency.[9] Pregnant women with anemia are at much greater risk of complications8 including premature delivery, low birth weight and possibly inferior overall neonatal health.[9]

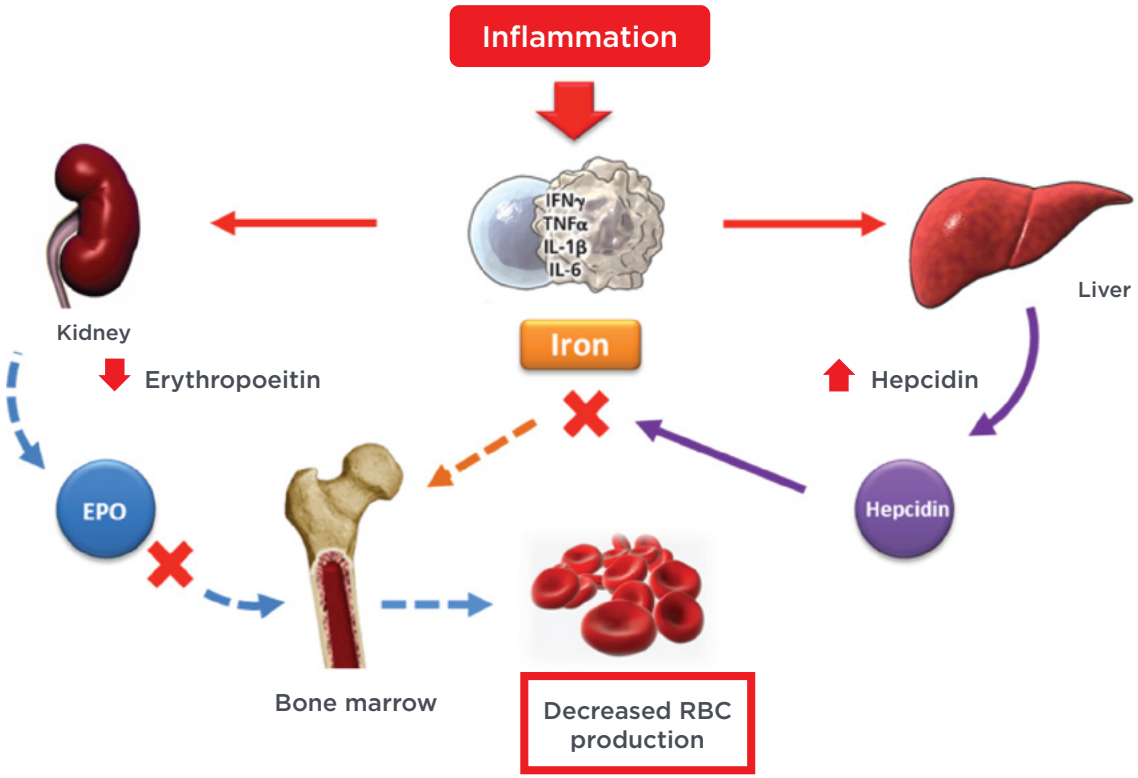
In children, IDA is associated with impaired cognitive performance, motor development, coordination, language development and scholastic achievement.10, 11 Because anemia adversely affects several immune mechanisms, it can also lead to increased morbidity in children due to the onset of infectious diseases.[6]

Anemia of Chronic Disease (ACD)

ACD is related to inflammatory conditions which trigger a complex chain of events limiting iron availability to the bone marrow. The low iron availability reduces production of hemoglobin and red blood cells, leading to functional iron deficiency and anemia (Figure 3).[12]

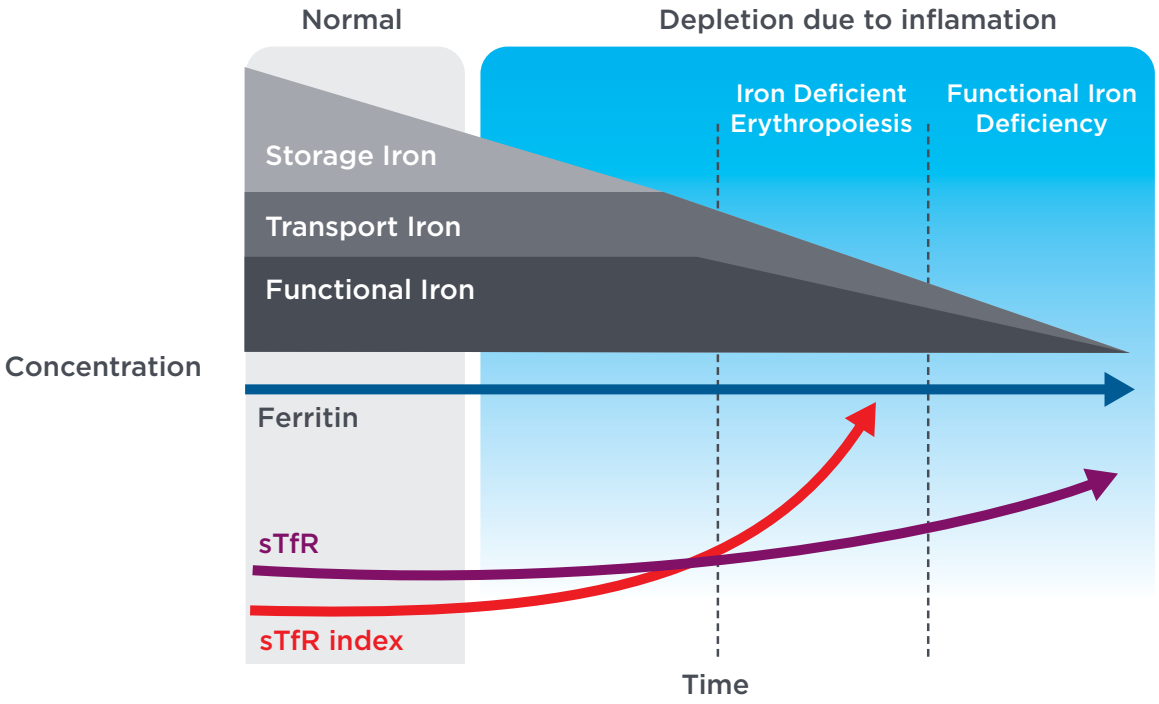
Chronic inflammation leads to activation of monocytes and macrophages, which release inflammatory cytokines. These cytokines, predominantly IL-6, suppress the production of erythropoietin (EPO) by the kidney and increase production of hepcidin by the liver. Hepcidin acts to inhibit the release of iron from the reticuloendothelial system.13 Both reduced EPO production and limited iron availability contribute to a decrease in RBC production. This functional iron deficiency finally leads to anemia of chronic disease.

Figure 3: Role of inflammation leading to functional iron deficiency in anemia of chronic disease



The diagnosis of ACD is challenging as it is often combined with iron-deficiency anemia (IDA). In patients with ACD, ferritin is not a good indicator of possible concomitant iron deficiency as it is an acute phase reactant and is often elevated in inflammatory conditions; therefore, it does not reflect the iron stores. In this case, the serum level of soluble transferrin receptor (sTfR)—and especially the sTfR index (combining sTfR and ferritin results)—are useful to identify IDA, particularly when IDA is present with ACD (Figure 4)[14]

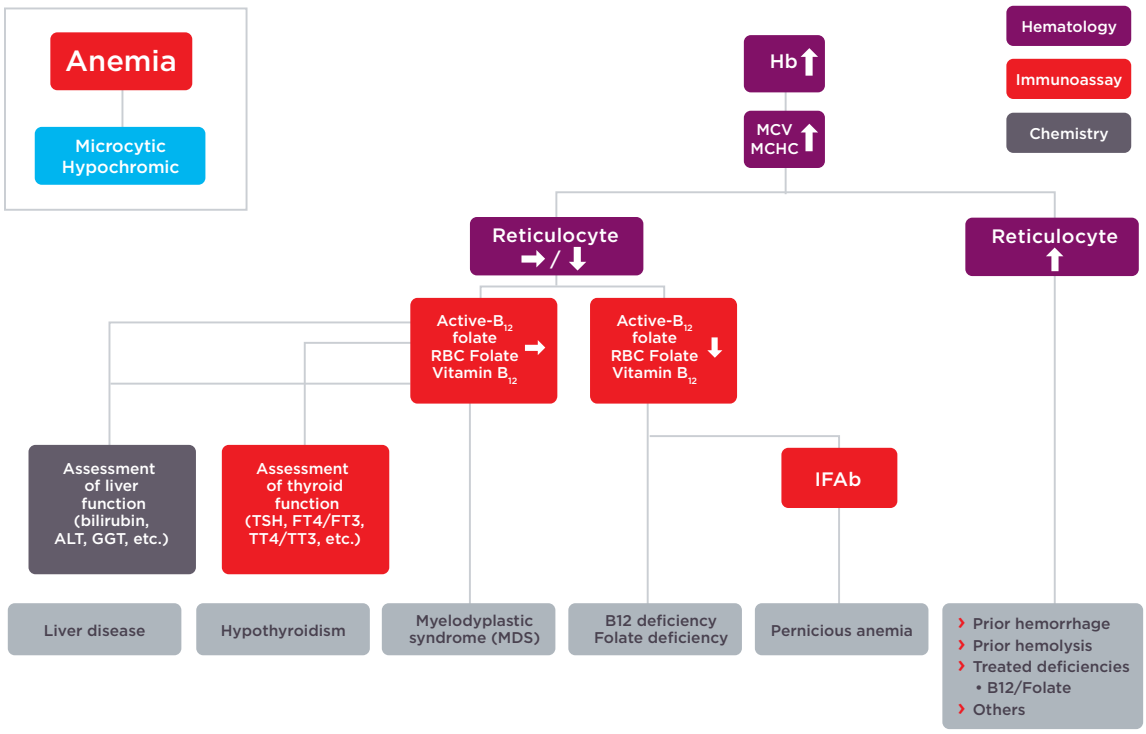
Figure 4: Level of ferritin, sTfR and sTfR index in the course of iron depletion in anemia of chronic disease combined with iron-deficiency anemia



sTfR Index=sTfR/log ferritin

Adapted from Suminen et al. Blood, 1998, 92;8;2934-2939.

Vitamin-Deficiency Anemia



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Vitamin-deficiency Anemia

Vitamin B12 and folate are essential components in the DNA synthesis, which is necessary for red blood cell formation. Prevention of low and deficient vitamin B12 status is of public health importance because it is associated not only with classical deficiency symptoms—such as hematologic abnormalities and irreversible neurological complications—but also potentially with a number of common age-related problems such as cognitive decline, cardiovascular disease, and bone fractures.[15]

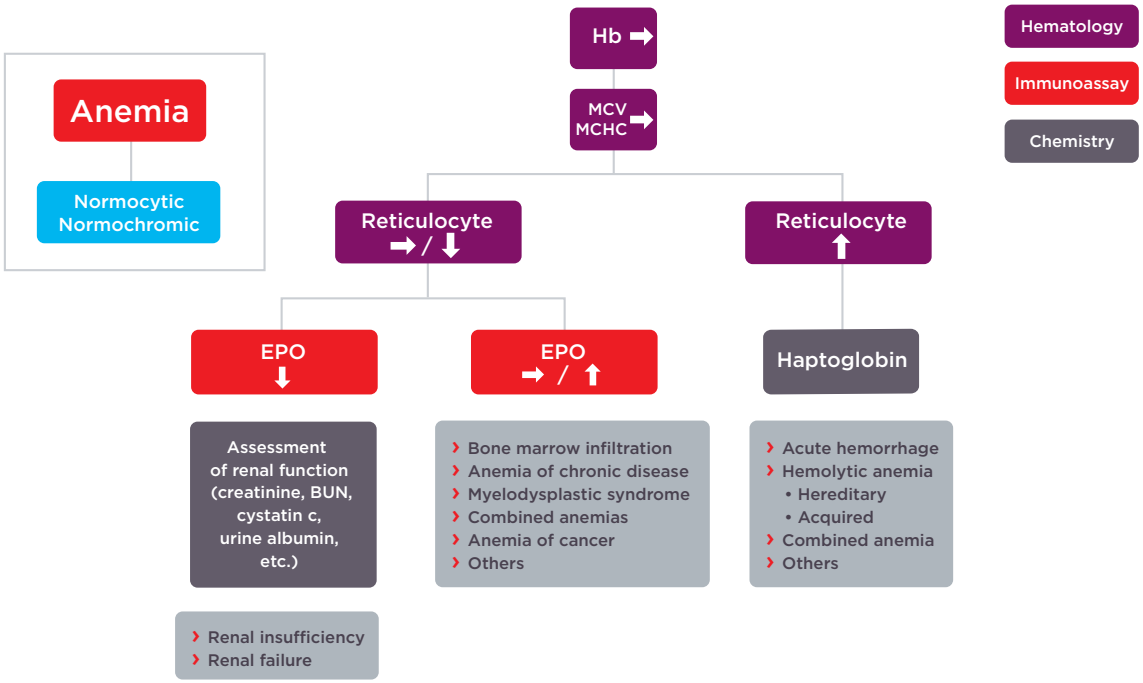
An initial RBC analysis using a hematology system is used to detect macrocytic RBC's, indicating possible vitamin deficiency. Further diagnostic testing for low-serum vitamin B12 or folate levels, as well as any clinical evidence of the deficiency, are traditional paths for the diagnosis of vitamin B12 or folate deficiency.[15] More recent, Active-B12 (holoTC) testing has been utilized as emerging evidence has supported the holoTC complex to be a preferable measurement in the clinical setting.[16]

Vitamin deficiency can be due to low uptake or to reduced absorption by the intestine. In pernicious anemia, impaired absorption of B12 is due to autoantibodies directed to the intrinsic factor, which is essential for B12 absorption. The detection of these intrinsic factor antibodies (IFAb) using an immunodiagnostic method is critical to diagnose pernicious anemia.[17]

Table 3: Symptoms and causes vitamin-deficiency anemia

Symptoms	Causes
› Weakness, pale skin › Shortness of breath, chest pain › Neurological symptoms • Ataxia • Paraesthesia of hands and feet • Diminished perception of vibration and position › Neuropsychiatric symptoms • Confusion and memory disturbances • Cognitive decline › Headache	› Inadequate dietary intake › Reduced absorption • Crohn's disease • Celiac disease • Pernicious anemia • Gastric surgery › B12 deficiency impedes folate uptake into RBCs • Liver disease and/or alcoholism › Increased utilization during pregnancy › Genetic disorder (MTHFR) › Drug therapy • Proton pump inhibitors • Histamine receptor antagonists

Anemia of Renal Failure and Anemia of Cancer



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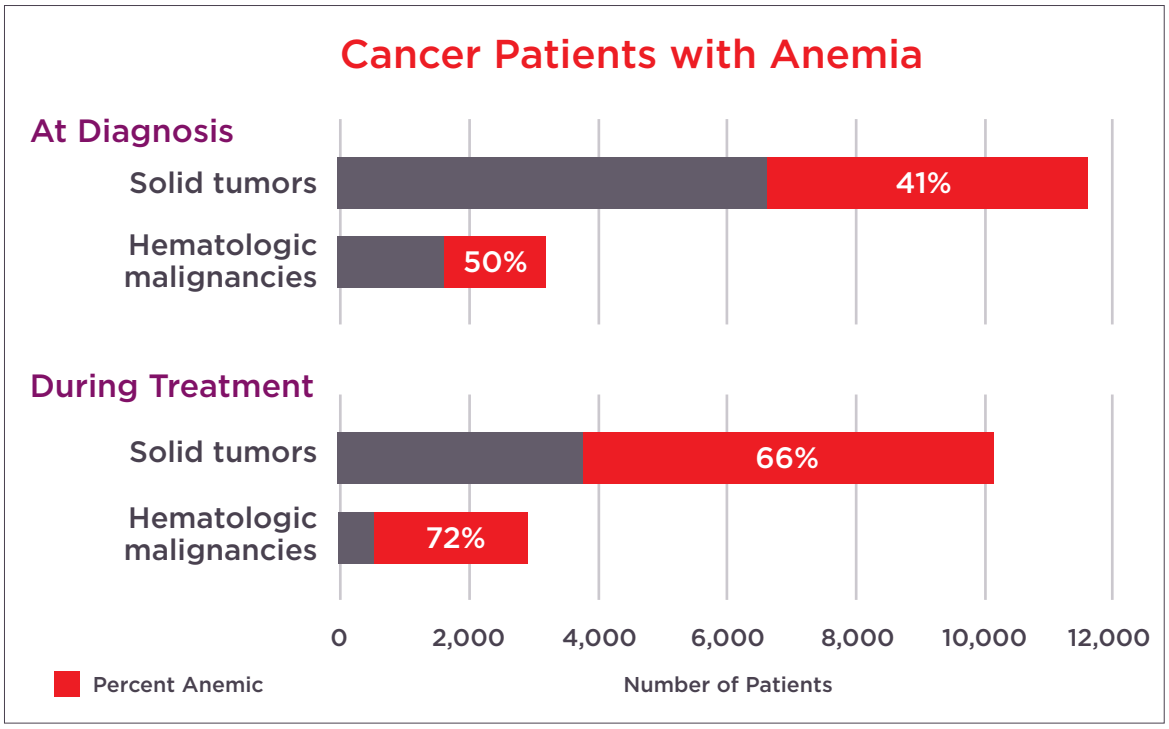
Anemia of Cancer



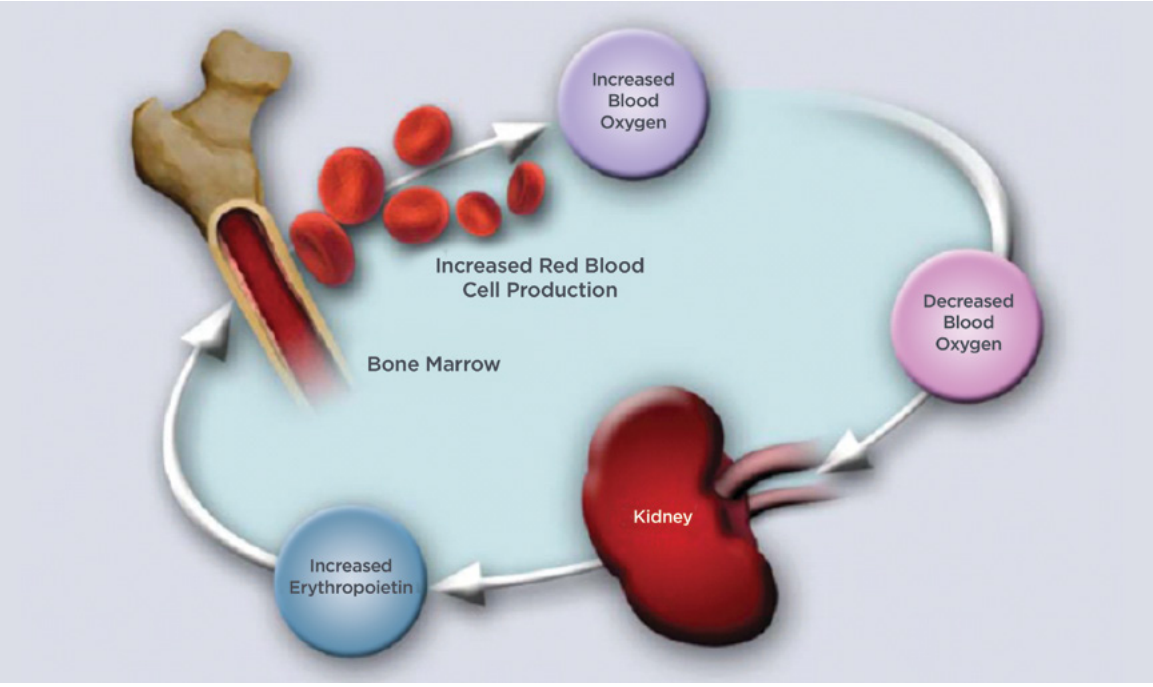
Birgegård et al. Eur J Haematol. 2006 Nov;77(5):378-86.

Anemia in cancer patients decreases the efficacy of therapy. In a review of 60 papers, Caro et al. examined the survival of cancer patients according to the level of hemoglobin and concluded that the presence of anemia increased the relative risk of death by 65 percent.[20] Appropriate management of cancer-related anemia, especially with the use of treatment involving recombinant human erythropoietin (rHuEPO), is therefore extremely important to increase survival of cancer patients.[18]

Anemia of Renal Failure

In patients with renal failure, anemia develops for several reasons. The predominant cause is inadequate production of erythropoietin (EPO) by the kidney, which normally is produced in response to decreases in blood oxygen levels (Figure 6). In addition to an EPO deficit, other causes may include a reduction in the typical life span of RBC from 120 days to 70 or 80 days. Patients with renal failure may have blood loss, inhibition of erythropoiesis by a chronic inflammatory state, lack of available iron stores or other nutritional deficiency.[21]

Figure 6: In healthy people, hypoxia stimulates production of erythropoietin by the kidney, which in turn stimulates red blood cell production. Declining kidney function adversely affects production of erythropoiesis and ultimately results in anemia



Anemia begins early in the course of declining kidney function. The severity of anemia in chronic kidney disease is correlated to the level of renal dysfunction.

Increased attention is being paid to understand and treat anemia among patients with chronic renal insufficiency. If left untreated, anemia has serious consequences in terms of the quality of life and increased risk of mortality, cardiac complications and rate of hospitalization.[22, 23] For every 1 g/dL decrease in hemoglobin, there is a 6% increase in risk of left ventricular hypertrophy.[22]

The development of recombinant human erythropoietin (rHuEPO) revolutionized the treatment of anemia of renal failure. Studies have shown that increased hemoglobin levels following rHuEPO treatment improved overall survival in hemodialysis patients.[24] However, the use of rHuEPO should be considered with caution, as the rate of cardiovascular events may increase.[25] Accurate determination of hemoglobin and the serum EPO level is useful to define optimal rHuEPO dose and also for monitoring therapy.[26]

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